THE YEAR BOOK *of* MEDICINE

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EDITED BY

PAUL B BEESON MD

CARL MUSCHENHEIM MD

WILLIAM B CASTLE MD

TINSLEY R HARRISON MD

GEORGE B EUSTERMAN MD

ROBERT H WILLIAMS MD



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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

PAUL B BEESON M.D

Ensign Professor of Medicine and Chairman of the Department of Internal Medicine Yale University School of Medicine Physician in Chief University Service Grace New Haven Community Hospital

The Chest

CARL MUSCHENHEIM M.D

Associate Professor of Clinical Medicine Cornell University Medical College

The Blood and Blood Forming Organs

WILLIAM B CASTLE, M.D

Professor of Medicine Harvard University Director Thorndike Memorial Laboratory Director Second and Fourth Medical Services Boston City Hospital

The Heart and Blood Vessels and the Kidney

TINSLEY R. HARRISON M.D

Professor of Medicine Medical College of Alabama Birmingham

The Digestive System

GEORGE B EUSTERMAN M.D

Emeritus Professor of Medicine University of Minnesota (Mayo Foundation) Chief of Medicine and Director Medical Education Sinai Hospital Detroit Michigan

Metabolism

ROBERT H WILLIAMS M.D

Professor and Executive Officer Department of Medicine University of Washington

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The articles abstracted herein are taken from journals received between May 1952 and May 1953

PART I

INFECTIONS

PAUL B BEESON MD

PART I

INFECTIONS

GENERAL CONSIDERATIONS

Bacteriophage as a Factor in Epidemiology and Bacterial Evolution Lysis of Diphtheria Bacilli by Staphylococcus Bacteriophage Strains of diphtheria bacillus differ widely in virulence growth characteristics and fermentation reactions and more than 60 different serologic types have been described The absence of any apparent evolution toward coarser and less fastidious growth requirements suggests the presence in nature of selective agents favoring multiplication of mutants regardless of general vigor of their growth L I Hewitt[1] has demonstrated that bacteriophage is such an agent Diphtheria bacteriophages are type specific and when added to a culture lyse most organisms leaving intact only mutant bacteria which differ from other cells in being resistant to the bacterial virus Organisms that grow out from the lysed culture are resistant to the lethal and lytic action of the bacteriophage Some of the phage resistant mutant strains are fully virulent and toxigenic Thus phage has been shown to be an agent capable of completely transforming biologic characteristics of a bacterial strain in a single subculture

Presence of carriers of avirulent diphtheria bacilli among fully immunized children cannot be dismissed as of no significance since in presence of bacteriophage avirulent strains can become virulent and might start an epidemic among unimmunized contacts since the proportion of immunized children is declining

Diphtheria phage is not the only kind that can alter the character of the bacilli The possibility that staphylococcus phage can affect diphtheria strains was studied Staphylococci are present in large numbers in nose and throat swabs so that almost all diphtheria strains have been in contact with staphylococci at some stage

(1) La t 2 72 73 A g 9 195

When Staphylococcus aureus bacteriophage No 47 was tested against various diphtheria strains there was no visible effect until after a few subcultures of the bacteriophage with diphtheria strains when filtrates were obtained which lysed the strains Thus staphylococcus phage had been converted to diphtheria phage

Action of staphylococcus bacteriophage against diphtheria bacilli may explain the wide variety of diphtheria strains encountered in infections since presence of staphylococci in nose and throat of diphtheria patients is common Staphylococcus aureus is perhaps not the only organism which can affect the growth of diphtheria bacteria Other bacteria present in nose and throat may cause mutation of diphtheria bacteria

Bacteriophages probably are important agents in modification of infections and epidemics and in evolution of bacteria

[This may be of great importance in elucidating the epidemiology of diphtheria Furthermore the principle involved may hold for relationships between other microbial flora of the body This should revive interest in bacteriophage as an agent of practical importance in human disease —Ed]

Induction of Streptomycin Resistance in Sensitive Hemophilus Influenzae by Extracts Containing Desoxyribonucleic Acid from Resistant H Influenzae Hattie E Alexander and Grace Leidy[2] (Columbia Univ) have induced resistance to 1 000 μg streptomycin/ml in normally sensitive H influenzae populations by exposure for 10 minutes to desoxyribonucleic acid (DNA) containing extracts isolated from a strain of type b H influenzae which had emerged resistant to 1 000 μg streptomycin/ml The nature of the process which induces resistance in all respects resembles the reaction which induces heritable changes in type specificity of H influenzae The resistant trait created by the experiment is heritable

The capacity of DNA extracts to induce resistance can be destroyed by exposure to the crystalline enzyme desoxyribonuclease The pattern of resistance brought out in a cell population by artificial means resembles the pattern displayed in sensitive populations after streptomycin selects out the spontaneously occurring mutants There is no possibility that the resistant mutants were spontaneous rather than induced

Only a small proportion (roughly 1 in 10 000) of the total cell population exposed is transformed to resistant cells The 10 and 1 000 μg streptomycin/ml environments select out cells

(2) J E pe M d. 97 17 31 Ja 1 1953

in which a comparable resistance has been induced by DNA $Sbsm_{1000}$ (Strain $Sbsm_{1000}$ is a type b H influenzae originally isolated from the cerebrospinal fluid withdrawn from a patient 24 hours after the start of streptomycin therapy) The change which enables bacterial cells to express resistance is induced within 10 minutes

Resistance to streptomycin is induced in a single step The incidence of spontaneously occurring H influenzae cells resistant to 1 000 μg/ml is 10^{-11}/bacterium/bacterial generation At least 1 000 million organisms are needed to predict the growth of one colony in the selective environment of Levinthal agar containing 1 000 μg/ml When sensitive H influenzae populations are exposed to DNA $Sbsm_{1000}$ one cell in approximately 10 000 will form a colony in the presence of 1 000 μg streptomycin/ml The incidence of the induced mutant is more than 1 000 000 times that of the spontaneously occurring resistant cell

The resistance induced by DNA containing extracts is an inherited trait Populations derived from each of two colonies selected out by 10 μg/ml and from each of two colonies which formed in 1 000 μg/ml were subcultured 11 times in Levinthal broth without streptomycin at 24 or 48 hour intervals and then retested for sensitivity to streptomycin There was no significant difference in the number of colonies formed when equal numbers of cells (100 200) of each of the four populations were seeded on Levinthal agar and Levinthal agar containing 1 000 μg/ml streptomycin

The study offers another example of the genelike action of highly specific desoxyribonucleic acids

[It is satisfying to watch the unfolding of knowledge such as this Previous work had shown that the desoxyribonucleic acid fraction of certain bacteria (pneumococcus Friedlander bacillus and H influenzae) is responsible for type specificity and capsule formation Now we see that the desoxyribonucleic acid from a drug resistant strain can influence a growing culture of drug sensitive organisms causing them to become permanently and heritably drug resistant —Ed]

Pathogenesis of the Jarisch Herxheimer Reaction Albert Heyman Walter H Sheldon and Lilian D Evans[3] (Emory Univ) review the clinical and experimental observations of this reaction It has long been known to occur during the treatment of syphilis and is generally attributed to the release of endotoxins or spirochetal breakdown substances following

(3) Brit. J V D s 28 50-60 M ch 1952

the initial administration of spirocheticidal agents These substances are thought to produce systemic manifestations such as fever chills and malaise as well as an exacerbation of syphilitic lesions The authors studies indicate the reaction may be a delayed hypersensitivity phenomenon similar to the tuberculin reaction

Herxheimer reactions occur not only in syphilis but also in other spirochetal diseases such as yaws Vincent s disease relapsing fever leptospiral diseases ratbite fever due to Spirillum minus and also in brucellosis glanders tularemia leprosy and anthrax after the appropriate specific chemotherapy Tuberculosis treated with streptomycin and para aminosalicylic acid has not been reported as showing any intensification of signs or symptoms In treatment of early syphilis reactions occur in 40% Of 44 patients with paresis 17 had fever and 6 had a transient increase in psychotic symptoms a total of 52% Only two of eight with tabes had a febrile reaction Two with meningomyelitis had more severe spinal cord manifestations Penicillin therapy caused death in patients with cerebral gumma There are no well authenticated instances of a serous Herxheimer reaction in cardiovascular syphilis and although possible this consideration is of no practical importance in the management of cardiovascular syphilis

The histologic study of syphilitic lesions in both patients and animals reveals that four to six hours after the beginning of penicillin treatment there is a transient acute inflammation with vascular congestion edema and infiltration with leukocytes After about 18 hours the acute process subsides and mononuclear cells appear Within 72 hours the lesion appears as it did before therapy A similar progression could be produced by the injection of immune serum known to contain immobilizing antibodies for Treponema pallidum With this suggestion that the reaction may be a hypersensitivity phenomenon ACTH was administered first in an attempt to block the reaction These experiments showed that ACTH was unable to inhibit the changes

It is believed that the reaction occurs only when spirochetes are destroyed by antibiotics chemotherapy or specific immune serum However destruction of spirochetes alone is not enough since there is no correlation between the incidence and severity of reactions and the number of treponemes pres

ent and destroyed The reactions occur with the same incidence in seronegative and seropositive primary syphilis The Herxheimer reaction is even more common in late syphilis in which spirochetes are few If the reaction is a hypersensitivity the incidence and severity would be related to the degree of hypersensitivity rather than to the number of antigenic organisms

With the exception of syphilis all of the diseases in which a Herxheimer reaction develops also have tuberculin type skin reactions Possibly in other diseases with a tuberculin type skin hypersensitivity such as lymphogranuloma venereum mumps coccidioidomycosis and histoplasmosis Herxheimer reactions may develop when effective chemotherapeutic agents are discovered Although the prevention of the Herxheimer reaction is important there is no known method which will accomplish this in neurosyphilis Prolonged therapy with bismuth may prevent the reaction in early syphilis but is not effective in neurosyphilis

Significance of Febrile Convulsions William G Lennox[4] (Harvard Med School) states that children with convulsive seizures that attend febrile illness form a substantial proportion of all young children brought to doctors b cause of seizures Although most pediatricians would consider these febrile convulsions innocent they mean any of the following (1) The fever may be a consequence of a spontaneous seizure the result of excessive muscular energy and heat (2) The seizure may be the result of excess hydration or of antibiotics given to combat an infection (3) The fever may be a seizure phenomenon the result of a paroxysmal seizure discharge in the region of the hypothalamus (4) The seizure may be due not to the fever but to bacterial toxins (5) The seizure may be the secondary result of cerebral pathology induced by an invasion of the brain by infectious organisms (6) The seizure may be the direct response of the child s organism to high fever in association with some infection or both fever and seizure may be a consequence of toxic action on brain cells

The seizure usually occurs while the temperature is rising or at its crest and usually when the rise is rapid Pediatricians have called febrile convulsions either simple or benign and have shunned the word epilepsy The benignity of a sei

(4) P d t 11 341 357 Apr l 1953

zure depends not on its name but on the severity of the convulsive movements the degree of apnea and cyanosis the duration of unconsciousness and whether the seizure is focal or generalized single or multiple

A study was made of 1 136 persons whose first convulsive seizure occurred in the first decade of life 298 had fever induced seizures (usually with subsequent nonfebrile seizures) and 838 had only nonfebrile seizures The two groups were compared with respect to sex age at first seizure presence of antecedent brain pathology and whether they were seen in clinic or office Extreme youth and absence of pathology were most often associated with febrile seizures In an augmented series of 407 patients with fever induced seizures 76 9% subsequently experienced nonfebrile seizures In 22% an interval of five years or longer separated the last febrile seizure from the first nonfebrile one

Febrile seizures are usually innocuous but if prolonged focal or attended by much cyanosis or protracted coma they may cause brain damage Of 392 patients who had brain injury in the first 10 years of life febrile seizures were blamed for the injury and the continuing epilepsy in 5 4% The genetic influence in children having fever induced seizures is unduly high Seizures uncomplicated by some acquired pathology of the brain tend to be short lived perhaps even self limited—limited by the stabilizing influence of age

[Perhaps we have not paid enough attention to convulsions associated with fever in children —Ed]

Sugar Content of Cerebrospinal Fluid in Diffuse Neoplastic Involvement of Meninges Henry W Dodge Jr George P Sayre and Hendrik J Svien[5] (Mayo Clinic) report four cases of neoplastic involvement of the meninges which presented difficult diagnostic problems and in which there was little or no sugar in the cerebrospinal fluid Correct presumptive diagnosis was made before death in three patients on this basis

Depression of sugar content of cerebrospinal fluid may be caused by infection of the meninges with pyogenic tuberculous fungous or yeastlike organisms Low concentration or absence of sugar in cerebrospinal fluid with adequate concentration of blood sugar may indicate carcinomatous sarcomatous or gliomatous involvement of the meninges

Mechanism of lowered sugar content in cerebrospinal fluid

(5) Proc Staff M et. M yo Cl 7 259 266 J ly 1952

in cases of diffuse meningeal carcinoma is not known The lesions may be accompanied by increase of protein and increase in cell count Possible factors include pleocytosis accelerated metabolism of neoplastic cells neoplastic involvement which may produce a blood brain barrier to such an extent that crystalloids are unable to cross the barrier merely because of mechanical blocking of the membranes and changes of protein values in the cerebrospinal fluid relative to blood protein values which may affect normal osmotic relations It is probable that accelerated cellular metabolism and simple mechanical blocking are the factors involved

[This is a pearl worth knowing since a clinical picture resembling that of tuberculous meningitis including low spinal fluid sugar content can be caused by some brain tumors —Ed]

CHEMOTHERAPY

Complications Induced by Antimicrobial Agents According to Maxwell Finland and Louis Weinstein[6] (Harvard Med School) the commonest untoward reactions to systemic antimicrobial agents are those appearing on the skin The most frequent skin lesion is a morbilliform eruption less frequent are the scarlatiniform urticarial vesicular and bullous eruptions which may be incapacitating The lesions may resemble erythema multiforme The most severe skin manifestation is exfoliative dermatitis which may follow the morbilliform or scalatiniform lesions when the offending agent is not removed it may be incapacitating and is sometimes fatal Use of the offending drug must be stopped Antihistamines may be helpful particularly in combating pruritus ACTH and cortisone may be of benefit in exfoliative dermatitis or bullous eruptions

Oral lesions sometimes described as ulcerative or vesicular stomatitis have been reported The chief symptoms are dryness burning soreness and itching of the mouth and tongue The buccal mucous membrane may be red and inflamed with or without vesicles Cheilosis and a black hairy tongue have appeared during antibiotic therapy Serious or distressing oral lesions are observed much more often with lozenges or troches than with oral or parenteral therapy

(6) N w E gl d J Med 248 220 226 F b 5 1953

Specific reactions of hypersensitivity to antimicrobial agents such as drug fever and contact dermatitis may occur The latter is observed particularly after penicillin and streptomycin therapy Applications of ointments and oily suspensions of various agents produce the highest incidence of local and systemic sensitization Angioneurotic edema Arthus phenomenon serum sickness and acute anaphylaxis may occur and are associated with fever urticaria eosinophilia and sometimes purpura arthralgia lymphadenopathy and splenomegaly

Two serious chronic systemic diseases i e periarteritis nodosa and disseminated lupus erythematosus have been attributed to antimicrobial agents

Gastrointestinal disturbances are most frequent after the use of broad spectrum antibiotics Nausea with or without vomiting and diarrhea of varying severity may follow oral administration The reactions are probably due to the direct irritating action of the agents on the bowel Some of the severe diarrheas have been associated with Staphylococcus aureus in the stool There have been some deaths from severe intestinal disturbances Acute monilial stomatitis and pharyngitis have been reported Liver damage has followed administration of aureomycin terramycin and to a lesser extent chloramphenicol

Obstruction to the urinary flow produced by massive crystallization has followed administration of sulfonamides Acute glomerular lesions or lower nephron nephrosis has followed the use of as little as 1 2 Gm of sulfonamides Polymyxin bacitracin and neomycin are primarily toxic to the kidney

Peripheral neuritis has followed prolonged treatment with broad spectrum antibiotic Paresthesias have been caused by streptomycin Damage to the vestibular branch of the eighth cranial nerve occurs most often with streptomycin therapy and damage to the auditory nerve has been more frequent with dihydrostreptomycin therapy Intrathecal administration of penicillin or streptomycin therapy is relatively safe The maximal amount that may be safely introduced into adults at any one time is 50 000 units of penicillin and 100 mg streptomycin Larger amounts may produce great increases in intracranial pressure hyperirritability twitching or convulsions and even death

Acute hemolytic anemia may follow administration of sulfanilamide Eosinophilia may occur late in antibiotic therapy Granulocytopenia and thrombocytopenia have been observed with streptomycin Aplastic or hypoplastic anemia has followed prolonged or repeated courses of chloramphenicol

Changes in the bacterial flora and appearance of new infections may occur durin or after administration of antimicrobial agents Localized ab cesses may occur at the site of penicillin injections usually due to Proteus vulgaris and Clostridium perfringens The most serious complications have been the emergence and increase in prevalence of organism that are resistant to most or all of the agents that have been used

Antimicrobial agents should be used only when definitely indicated They should not be used in simple diseases lest a mild condition be converted into a serious and potentially fatal one

[The authors with wide experience in chemotherapy of infection have compiled a useful listing of the various toxic manifestations of the various agents now in use —Ed]

Comparison of Antibacterial Activity of Single and Combined Sulfonamides Louis Weinstein and Edward B Murphy[7] (Boston Univ) confirm and extend the reports of Schweinburg and Rutenberg that combinations of some sulfonamides are less bactericidal than the single agents composing the mixture Combining of sulfonamides in mixtures containing two or three of these agents may produce three types of change in their antibacterial activity as compared to the effect of the drugs used alone an additive potentiating or depressing effect The results with any given mixture were totally unpredictable This raises considerable question as to the usefulness of combined sulfonamide therapy in human infections

There was a high incidence of depression of antibacterial effect when sulfonamides were combined against gram positive organisms Sulfathiazole tended to increase and sulfamerazine to decrease the lethal effect of combined sulfonamides on gram negative bacteria On the other hand the addition of sulfadiazine increased the bactericidal potency for gram positive bacteria The combination producing the greatest depression of antibacterial activity for all organisms appears to be one containing sulfamerazine sulfadiazine and sulfathiazole

(7) Proc Soc Exper Biol & Med 80 519 5 2 July 1952

These results suggest that combinations of sulfonamides may have little clinical usefulness in many instances

[Nowadays when the drug houses are offering a variety of combinations of sulfonamide derivatives it is disturbing to be shown that antibacterial activity can be diminished by mixing these agents—Ed]

Mode of Action of Antibiotics Penicillin and Streptomycin W W Umbreit and E L Oginsky[8] (Rahway N J) pose three questions At what vulnerable point in the biochemistry of the cell does the antibiotic attack? What is the basis for the specificity that permits their use in vivo? What biochemical changes occur when resistance to the antibiotic develops?

Before the drug can act it must be adsorbed When penicillin is adsorbed by the bacterial cell about 750 molecules are bound in a nonexchangeable manner by a binding component which is manufactured by the cell during growth This binding component is an enzymatic process active in the surface of the cell which may be occupied or inactivated by penicillin with the result that glutamate transport is prevented and ribose nucleic acid synthesis is inhibited The cell continues to take up phosphorus and forms nonamino nitrogenous compounds at the expense of protein synthesis Perhaps animal cells do not have this binding component and are therefore *immune to the growth impairing effects Resistance may* be acquired by a previously sensitive organism if it makes one or more of the following changes

1 Becomes impermeable to the drug
2 Develops a reaction destroying drug
3 Alters its metabolism so that
   a) with a competitive drug it makes more substrate
   b) employs another path to the product(s) of the inhibited reaction
4 Alters the sensitive enzyme(s) so that it is no longer sensitive

The most probable mechanism of resistance is 3b

Streptomycin has been found to inhibit the oxalacetate pyruvate reaction thus blocking the terminal respiration system of susceptible organisms Why does it not do this in the animal cell as well as in the bacterial cell? Apparently the site *of terminal respiration is in the mitochondria and the mitochondria* of animal cells present a surface barrier so that no streptomycin penetrates them whereas the bacterial cell is permeable and permits entry of the lethal streptomycin When

(8) J Mt Sinai Hosp 19 175 184 May June 1952

ever the bacterial cells grow in the presence of streptomycin it may be demonstrated that the oxalacetate pyruvate reaction is not present in these cells Apparently alternative metabolic pathways for respiration have been achieved

Both streptomycin and penicillin act by combining with a specific (but different) enzyme system in an irreversible manner When resistance to the antibiotic develops that particular enzyme system is found to be by passed Their usefulness in vivo depends on their specificity

Experimental Approach to Problem of Treatment Failure with Penicillin I Group A Streptococcic Infection in Mice Harry Eagle[9] (Nat l Inst of Health) states that large dosages of penicillin continued for long periods of time may sometimes *fail* to cure infections caused by organisms which judged by in vitro sensitivity should have been readily controlled This has been especially true of subacute bacterial endocarditis in which 10-40% of patients are *usually* not cured after penicillin therapy and in syphilis in which 5 15% of patients are not cured after any schedule of penicillin therapy Factors responsible for these paradoxical treatment failures were studied in mice by inoculating the muscles with group A streptococci and then treating with penicillin

In the freshly inoculated animal penicillin exerted a rapid bactericidal action effecting sterilization and cure in 1½ to 6 hours however in animals treated 12 24 hours after inoculation a single injection of procaine penicillin in oil with monostearate or four injections of the sodium salt no longer sufficed Its bactericidal action was so slow that daily treatment with the procaine suspension had to be continued for six to eight days to effect sterilization and cure The following are possible explanations for the retarded bactericidal action of penicillin in older infections

1 Impaired host participation is an unlikely factor *the* therapeutic action of penicillin rests primarily on its direct bactericidal action and continues for just as long as the drug remains at effective concentrations at the focus of infection The possibility that the host factor has been impaired was excluded because mice which had been infected 24 hours earlier were re inoculated in another site immediately before treatment the bactericidal action of the drug although not

(9) Am J M d 13 389 399 O tobe 1952

apparent in the old site was promptly manifest in the freshly inoculated site

2 Number of organisms when the inoculum was varied from 10 000 to 50 000 000 organisms had no demonstrable effect on the rate of bactericidal action of penicillin This factor is not important because when animals were allowed to go for 24 hours before treatment there was the usual striking reduction in the rate of the drug s bactericidal action despite the fact that the site at the time of treatment contained fewer viable organisms than some of the freshly inoculated sites successfully treated the day before

3 Diffusion of penicillin into the muscle site is not considered an important factor since massive doses of sodium penicillin were no more effective in treating a 24 hour infection than a single injection of procaine salt in oil If the penicillin concentration was 10 000 times the effective level immediately adjacent to the infected site enough would eventually diffuse into the area to effect a bactericidal action

4 The metabolic activity of the organisms is a factor which to an important degree conditions the therapeutic action of penicillin The factor which determines the susceptibility of dividing bacteria to penicillin is probably not the actual continuing multiplication of the organisms but rather the fact that they are actively metabolizing a favorable medium The greatly reduced therapeutic action of penicillin in the older infections is due to the fact that the organisms are no longer metabolizing as actively in the inflammatory focus

In an early infection multiplication is rapid and metabolism of the organisms active they are highly susceptible to the direct bactericidal action of penicillin As the organisms continue to multiply they probably exhaust the surrounding tissue of nutrilites faster than they can be supplied by the blood stream The ultimate inflammatory reaction with edema tissue necrosis cellular infiltration and capillary thrombosis would accentuate this by limiting the diffusion of foodstuffs into the focus of infection The leukocytes in the inflammatory focus compete with the bacteria for nutrilites and metabolic products toxic to the bacteria reduce their metabolic acti[illegible]

[illegible] wn to affect only actively growing

ce[illegible] on resting cells the organisms

probably become less susceptible to its bactericidal effect for the very reason that they are growing and multiplying only slowly in an unfavorable environment

[The findings in Eagle's beautifully designed experiments have been of great value as guides to our present clinical practice in penicillin therapy Here is a reasonable explanation for some treatment failures In the next paper he and his associates provide a basis on which we can make logical decisions regarding type of penicillin and dosage required in various situations —Ed]

"Continuous" vs "Discontinuous" Therapy with Penicillin Effect of Interval between Injections on Therapeutic Efficacy According to Harry Eagle Ralph Fleischman and Mina Levy[1] (Nat'l Inst of Health) there is considerable experimental evidence that the therapeutic action of penicillin rests largely on its direct bactericidal action and that the factor that primarily determines its therapeutic efficacy is the total time for which the drug remains at effective levels at the focus of infection It is not necessary however that effective levels be continuously maintained to effect cure Although the rapid bactericidal action stops as soon as the concentration falls below the effective level the surviving bacteria do not immediately resume multiplication Cure of disease can be achieved in man by schedules of treatment in which penicillin is given so infrequently that for a large portion of the treatment period there is no demonstrable penicillin in the blood

A study was made of the time dosage relation in an infection with group A streptococci in normal nonimmune mice Results were consistent with the thesis that the most rapidly effective schedule of penicillin administration is one that continuously provides the maximally effective concentration against a particular organism at the focus of infection the primary determinant of therapeutic activity is the time for which the drug remains at effective concentrations at the focus of infection a penicillin free interval between injection prolongs the total duration of treatment necessary for cure and if that interval is so long as to permit the interim remultiplication of surviving bacteria larger amounts of treatment and a longer penicillin time are required to effect cure than would otherwise have been necessary

Continuous levels of penicillin high enough to effect a concentration at the focus of infection in excess of that necessary to kill the organism at the maximal rate can be provided

(1) N w E gl d J M d 248 481 485 M 19 1953

by a continuous drip or small doses of aqueous sodium peni cillin repeated at intervals of about two to four hours The serum concentration of penicillin should be 5 20 times the sensitivity level of the organism

In choosing between the many dosage forms of penicillin which vary widely in their rate of absorption and therefore in both duration of action and magnitude of serum concen trations that they afford the physician must consider the ap proximate penicillin sensitivity of the presenting organism and the location of the infectious process A serum concentra tion 10 times the sensitivity level will usually provide the maximally effective concentration at the site of infection and the physician can use the schedule of treatment that at the greatest convenience to the patient and himself will provide such a serum level more or less continuously For example an organism killed most rapidly by 5 units/cc would compel the physician to use massive doses of aqueous sodium penicillin at fairly frequent intervals for an organism requiring 0 5 units/cc 600 000 units of aqueous procaine penicillin repeated once or twice daily would probably suffice for organisms killed most rapidly by about 0 1 0 2 units/cc or less 1 200 000 units of procaine penicillin in oil with monostearate repeated every 4 days would ordinarily be an effective regimen and for highly sensitive organisms such as group A streptococci Treponema pallidum or gonococci the even more slowly ab sorbed dibenzylethylenediamine salt administered every 10 days would probably suffice In each case if diffusion of peni cillin into the focus of infection is limited by anatomic con siderations it becomes necessary to use a more rapidly ab sorbed preparation providing higher concentration in the serum than would otherwise be required

Some Clinical and Laboratory Observations on the Hydri odide of Diethylaminoethyl Ester of Penicillin G (Neo penil®) Margaret E Grigsby Thomas H Haight and Max well Finland[2] (Harvard Med School) describe neo penil® in aqueous suspension as a repository preparation of penicillin Significant concentrations of penicillin appear in the lung and sputum and other body fluids after parenteral injection It was given to 42 patients aged 28 80 half of whom had acute pneu monia 13 due to pneumococci including 1 with bacteremia

(2) New England J Med 247 807 812 N 20 1952

and the rest due to staphylococci streptococci Hemophilus influenzae or Klebsiella pneumoniae Most of the other patients had chronic nontuberculous bronchopulmonary infections With few exceptions neo penil® was given every 12 hours in doses of 500 000 units suspended in 1 5 cc distilled water Total dose for each patient ranged from 3 to 25 Gm over 2 12 days

Concentrations of penicillin in sputum and the ratio of these concentrations to those found in the plasma were higher after neo penil® than after similar amounts of aqueous suspensions of procaine penicillin or solutions of potassium penicillin G The clinical response to neo penil® in patients with acute pneumonia due to penicillin sensitive organisms was in every way comparable to that generally seen after treatment with 100 000 250 000 units of aqueous salts of penicillin every three to four hours In chronic bronchopulmonary infection the immediate effects were uniformly favorable in patients with fever and symptoms of acute exacerbations and generally favorable in the chronic suppurative process Fever subsided more gradually in chronic disease The sputum changed from thick and purulent to mucoid and much less purulent

Although the data do not prove any superiority of neo penil® over procaine penicillin or the soluble salts of penicillin G the higher concentrations of penicillin in sputum during neo penil® therapy and apparent easier tolerance of intramuscular injections suggest that it deserves a further trial in bronchopulmonary infections due to penicillin susceptible organisms

[This preparation seems to be superior to other penicillins in certain types of chronic bronchopulmonary suppuration but is certainly not required for successful treatment of pneumococcic pneumonia There appear to have been more anaphylaxis type reactions (including a few fatalities) with it than with other penicillins so some caution should be used in choosing it Should not be injected intravenously—Ed]

Lack of Interference of Aureomycin with Penicillin in Treatment of Pneumococcic Pneumonia James J Ahern and William M M Kirby[3] (King County Hosp Seattle) point out that certain bacteria are destroyed more slowly in vitro when exposed to the combination of penicillin and aureomycin chloramphenicol or terramycin than when exposed to penicillin alone Antibiotic antagonism has also been observed in experimental mouse infections Lepper and Dowling reported

(3) A M A A h I t Med 91 197 203 F bruary 1953

a higher mortality rate for patients with pneumococcic meningitis who received both penicillin and aureomycin than for a control group treated with penicillin alone Aureomycin may possibly have interfered with the early bactericidal action of penicillin necessary for rapid destruction of pneumococci With infections in other parts of the body however phagocytosis is more effective than in the subarachnoid space and actual killing of bacteria by the antibiotic is not so essential

Response of 25 patients with pneumococcic pneumonia to penicillin and aureomycin was compared with that of 25 treated with penicillin alone Most of the patients were elderly and debilitated and many were alcoholics The pneumococci were obtained by blood culture or were the predominant organism in sputum cultures All patients were given penicillin G procaine intramuscularly 600 000 units on hospitalization and 300 000 units every 12 hours thereafter Aureomycin was given orally 250 mg every six hours Two patients who were unable to swallow the capsules when first admitted received 200 mg aureomycin intravenously every 12 hours until they could tolerate oral administration Therapy was continued as long as the clinical course warranted usually five to seven days

Half the patients in each group were afebrile by the third hospital day (average 36 hours) The factors of age general debility and alcoholism accounted in large part for the high incidence of bacteremia (34%) complications (24%) and deaths (12%) all of which were equally distributed between the two groups From the standpoint of symptomatic improvement temperature response disappearance of pulmonary infiltrations and length of hospitalization results were essentially the same in the two groups There was no evidence of antibiotic antagonism

Pneumococcic meningitis is probably one of the few diseases in which interference of the broad spectrum antibiotics with penicillin is of clinical importance In pneumococcic pneumonia the situation is quite different In the lungs phagocytosis is highly effective beginning early in the course of the illness and cure of the disease is not dependent entirely on the bactericidal action of the antibiotic as in the cerebrospinal space

[The authors thesis in the first paragraph seems a logical explanation for the different results in pneumococcic meningitis and pneumonia —Ed]

Changes in Bacterial Sensitivity to Aureomycin and Chloramphenicol in the Course of the Past Three Years are discussed by S Stanley Schneierson[4] (Mount Sinai Hosp New York City) In light of experience with older chemotherapeutic agents a survey of sensitivity to aureomycin and chloramphenicol of different bacteria isolated from pathologic material was undertaken to determine whether any increase in bacterial resistance had developed within the three years after introduction of the drugs Gradual emergence of resistance to the drugs was found in various organisms but a statistical study by means of the chi square test showed that only the increasing bacterial resistance of Escherichia coli proteus Staphylococcus aureus and Streptococcus faecalis to *aureomycin was significant*

Many strains of bacteria have become resistant to streptomycin and the sulfonamides and staphylococci have become increasingly resistant to penicillin Terramycin was not investigated since resistance of most bacteria to terramycin closely parallels that to aureomycin

Marked variation in susceptibility to these antibiotics shown by individual members of some groups strongly emphasizes necessity for performing sensitivity tests in order to select the most effective antimicrobial agent against these micro organisms Development of resistant forms limits the value of available therapeutic agents against a number of infectious organisms capable of producing serious disease

[The trend demonstrated here is worrisome We will have to continue to find and use new antibiotics in order to keep ahead of the tendency of many pathogenic micro-organisms to become resistant to the agents in current use —Ed]

Some Laboratory and Clinical Observations on New Antibiotic Erythromycin (Ilotycin) Fordyce R Heilman Wallace E Herrell William E Wellman Joseph E Geraci with Dorothy Rose and Edward Warren[5] reporting preliminary studies on the antibiotic state that generally the gram positive bacteria are more sensitive than the gram negative Hemophilus pertussis is one of the gram negative bacteria that is sensitive Group A hemolytic streptococci and Diplococcus pneumoniae are very and corynebacteria the most sensitive Erythromycin is bactericidal in vitro for bacteria sensitive to its action

Proper average dose of erythromycin orally for adults is

(4) J Lab & Cl Med 40 48 57 J ly 1952
(5) P oc St ff M et M y Cl 27 285 304 J ly 16 195

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0 4-0 5 Gm every six hours If gastrointestinal irritation appears dosage may be reduced to 0 3 Gm The drug must be given every six hours since the serum concentration usually begins to decline sharply in four to six hours Such gastrointestinal symptoms as nausea vomiting and diarrhea appear when the dose is as high as 0 75 1 0 Gm

Studies in persons with noninflamed meninges indicate that little of the erythromycin enters the cerebrospinal fluid It cannot however be concluded that erythromycin does not traverse the blood brain barrier when there is inflammation When there are therapeutically effective amounts of erythromycin in the serum the antibiotic diffuses into the ascitic fluid

Erythromycin is concentrated in the liver and excreted readily in the bile in a biologically active form Large amounts of the drug appear to be constantly excreted in the urine

There apparently is no cross resistance between erythromycin and other antibiotics and organisms resistant to them may be fully susceptible to erythromycin

Erythromycin will be effective in treatment of infections with strains of Micrococcus pyogenes which are resistant to other antibiotics There is both laboratory and clinical evidence that certain microbes may gradually become resistant to this antibiotic

Results of preliminary clinical trials in a variety of infections were encouraging but more clinical studies must be carried out before the final value of erythromycin can be assessed

[Here is a useful new antibiotic effective against penicillin resistant staphylococci and so far without notable toxicity Unfortunately many organisms rapidly develop resistance to it —Ed]

Disturbance of Normal Bacterial Ecology by Administration of Antibiotics with Development of New Clinical Syndromes According to David T Smith[6] (Duke Univ) evidence is accumulating which shows that the complex balance existing among micro organisms constituting the normal flora of the body is disturbed by prolonged administration of the newer antibiotics This may result in development of secondary vitamin deficiencies or the evolution of new infectious disease syndromes The struggle for survival among animal species has *its counterpart in the world of microscopic organisms* This antagonism is sometimes seen between different strains of a

(6) Ann. Int. Med 37 1135 1143 Dec mbe 1952

single species but more often between species of different genera Most of the known antibiotics which kill bacteria are produced by fungi whereas antibiotics derived from bacteria kill fungi

The infant is free from bacteria when it begins its passage through the birth canal Some bacteria are acquired during birth and within a few days of birth the child has acquired a flora which is practically identical with that of the adults in its environment.

Complications in the oral cavity are unusual after either oral or parenteral therapy with penicillin but local treatment with lozenges powders or sprays may be followed by increased redness or edema and secondary infections with yeasts and molds which give rise to the clinical picture of hairy tongue or black tongue Although penicillin may accelerate the growth of Candida albicans var stellatoidea and Pseudomonas aeruginosa the primary mechanism is probably the elimination of the normal inhibitors of yeast and molds such as the gram positive cocci The initial improvement after the use of penicillin in chronic bronchitis chronic bronchiectasis and chronic pulmonary abscess is dramatic but after a few weeks of continuous therapy the sputum increases and the original predominant gram positive flora has been replaced by gram negative bacilli of the type usually found in the intestinal tract Klebsiella pneumoniae and Ps aeruginosa are dangerous secondary invaders Serratia marcescens is occasionally isolated This supposedly nonpathogenic organism has apparently become pathogenic

Before the introduction of antibiotics C albicans was known to produce thrush in infants and debilitated adults bronchitis and occasionally pneumonitis but it almost never invaded the internal organs With the use of antibiotics C albicans infections are encountered more often Serious infections of the mouth and pharynx vagina and lungs are seen and fatal infections after invasion of the internal organs are being recognized

The normal microbiologic flora of man is varied and complex but seems to have been stabilized by a long process of evolution in such a manner that the organisms have a happy home and man is not injured Apparently constant and deadly warfare is carried on between gram positive cocci and gram

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negative bacilli and between both these groups and the yeast and moldlike fungi The precarious balance maintained by the normal ecologic flora is upset easily by administration of antibiotics The newer antibiotics with broad coverage spectrums should not be administered for more than one week at a time unless the agent causing the *infection has been identified and indications for prolonged therapy are obvious*

[There is no question that superinfections occur as a result of disturbances of microbial equilibriums by chemotherapeutic agents Examples are *pulmonary infections with Friedlander bacilli and penicillin* resistant staphylococci following penicillin therapy The case for monilial superinfections seems to me less definitely established There is no question that monilia often become more abundant in the oral respiratory or intestinal tracts after therapy with various antibiotics but mere increase in number does not mean symptomatic infection (See Kligman this YEAR BOOK p 29) —Ed]

Oral Undecylinic Acid in Prevention of So called Monilial Complications Secondary to Use of Aureomycin, Chloramphenicol and Terramycin David C Mountain (Marquette Univ) and Frederick P Krumenacher[7] (Columbia Hosp) *consider monilia the etiologic agent in the pruritus ani* glossitis pharyngitis vaginitis and pruritus vulvae which are common after the use of wide spectrum antibiotics They therefore tried undecylinic acid orally to prevent such complications in patients receiving antibiotics because its local use as a fungicidal agent is well established and because of its low toxicity in large doses internally It was given in doses ranging *from 1 capsule (0 44 Gm) to 3 capsules (1 32 Gm) with* each dose of the selected antibiotic three times daily after meals None of the 20 patients who was given one of the antibiotics and undecylinic acid by mouth simultaneously had side reactions Of 42 patients given undecylinic acid three days after the antibiotic was started 2 had pruritus ani a 3 2% failure in all those given the acid orally Of 45 controls not *given undecylinic acid 12 (26 7%)* had one or more of the monilial complications

Undecylinic acid did not prevent recovery of Monilia albicans from the stool or the pharynx in a high percentage of patients who received the drug It was not proved that the drug acts as a fungicidal agent but no clinical thrush occurred during its use *Undecylinic acid may be of value in treating these* complications after they have appeared

[These authors are convinced that symptomatic monilial infections

(7) Am J M S 225 74 80 M ch 1953

do occur commonly with antibiotic therapy and that they are largely preventable Contrast this with the opinion expounded in the next article and also with that of Dearing and Heilman (this YEAR BOOK p 41) —Ed]

Are Fungus Infections Increasing as Result of Antibiotic Therapy? Albert M Kligman[8] (Univ of Pennsylvania) points out that the newer wide spectrum antibiotics are apparently more troublesome than penicillin as a cause of undesirable side reactions The e include sore mouth and throat stomatitis glossitis black hairy tongue perleche diarrhea anal and vulvar pruritus and genitocrural lesions The belief that these reactions are manifestations of moniliasis and not of other diseases with similar features rests largely on the readine s with which Candida (Monilia) albicans may be isolated from persons with such reactions This evidence is not sufficient The fungus can be isolated from many persons taking antibiotics whether they have symptoms or reactions of any kind The diagnosis of moniliasis in a person with some unfavorable reaction therefore requires more than a mere demonstration of the organism

Thrush a form of localized mucous membrane moniliasis is the commonest expression of this disease The typical lesion is a whitish film or plaque which is curdy or membranous Classic thrush is uncommon after antibiotic therapy The diagnosis of moniliasis in tissues not accessible to direct inspection such as the lungs is difficult Short of a biopsy it is almost impossible to establish the diagnosis of bronchopulmonary moniliasis Further complications arise because of the frequency with which C albicans establishes itself in pathologic tissue as a secondary invader Many ca es of nonfatal bronchopulmonary moniliasis recorded in the literature cannot be accepted as authentic becau e in numerous instances other primary pulmonary diseases were present and in some diagnosis was based on isolation of the organism alone

The wide spectrum antibiotics were not found to enhance the growth of C albicans in vitro nor to potentiate mycotic disease in animals with experimental moniliasis blastomycosis histoplasmosis coccidioidomycosis and sporotrichosis

A small number of well authenticated cases of generalized fatal moniliasis (exclusive of generalized cutaneous moniliasis) have been recorded in which the authors stress the possible etiologic role played by prolonged antibiotic therapy The

(8) J.A.M.A 149 979-983 July 12 1952

existence of a large quantity of potentially pathogenic organisms in a severely ill person predisposes to infection Fungi which ordinarily have a low degree of virulence may find conditions favorable for invasion when the host defenses are depressed by such factors as serious disease malnutrition surgical trauma or old age Antibiotic therapy has made it increasingly rare for patients with fatal disease to die of a terminal bacterial infection In some instances fungi will take over the role formerly played by the bacteria in bringing about death

It may be that moniliasis has actually increased as a result of antibiotic therapy Physicians are probably seeing more cases of true thrush than formerly particularly in debilitated aged persons This may be simply an expression of the opportunistic pathogenicity of C albicans Considering the extraordinarily common use of antibiotics however even this localized type of infection is fairly uncommon

In most cases after antibiotic therapy elimination of susceptible organisms and their replacement by nonsusceptible ones has no clinical significance The problem of antibiotic resistance however acquires a greater significance in respect to those organisms that are not intrinsically resistant such as coagulase positive staphylococci and hemolytic streptococci The latter are potentially highly virulent and the increasing incidence of resistant strains has serious clinical implications This problem has a far greater significance than that of superinfection with fungi

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ACTH AND CORTISONE THERAPY

Waterhouse Friderichsen Syndrome Treated with Cortisone Report of Two Cases is presented by G E Breen R T D Emond and R V Walley [9] This syndrome a fulminating meningococcic infection is characterized in life by collapse and hemorrhages into the adrenal gland No other infection is so consistently or so quickly fatal Death sometimes results within 12 hours and commonly within 24 The patient usually a child under age 2 has apparently recovered from a cold when he suddenly becomes restless and fretful and refuses

(9) Lancet 1 1140-1142 June 7 1952

food There may be vomiting or diarrhea rigor a convulsion or rapidly developing delirium Pronounced cyanosis appears and the respiratory rate increa es Within a few hours purpura and ecchymoses are seen and collapse rapidly supervenes It is noteworthy that there may be no signs of meningitis and that the cyanosis and polypnea often suggest pneumonia Unless a lumbar puncture is done pneumonia will be diagnosed The cerebrospinal fluid may (rarely) show few or equivocal changes and prove sterile on examination and culture although the organisms can usually be recovered from the blood

The case fatality rate is high despite antibiotic therapy According to Kinsman and co workers in 200 cases reported up to 1946 there were about 20 recoveries Nelson and Goldstein reported two cases in 1951 in which cortisone appeared to be strikingly effective Remarkable improvement occurred in one within four hours after the initial dose of cortisone On the basis of the two cases reported here Breen *et al* concluded that cortisone is of great value in this syndrome

CASE 1 —Girl 2½ was hospitalized because of vomiting and intermittent delirium for one day Examination revealed cyanosis extreme restlessness slight neck stiffness and numerous purpuric spots on the skin Turbid fluid was obtained on lumbar puncture Sulfamezathine was given intravenou ly and sulfadiazine orally When pneumococci were found in the cerebrospinal fluid aureomycin 0 5 Gm every four hours was substituted for the sulfadiazine The next morning the child had more purpuric pots and was deeply cyanosed and incontinent The pulse rate was 180/minute and the blood pressure 88/38 mm Hg The infant vomited the aureomycin and was given sulfamezathine and penicillin intramuscularly Re examination of the cerebrospinal fluid showed Neisseria meningitidis Cortisone was given in doses of 25 mg every 6 and then every 12 hours Within a few hours the blood pressure ro e to 95/40 mm vomiting ceased and no further hemorrhages were noted The next day temperature was normal cyanosi had disappeared and she had recovered consciousness For the next two days the patient did well but on the third day after cortisone therapy was begun she became worse and died the following day

Autopsy revealed petechial hemorrhages on the small bowel serosa and hemorrhages in both adrenals and the cerebral cortex

Although cortisone did not save the patient s life there can be no doubt that it prolonged it for several days and but for the cerebral hemorrhages the child would have recovered

CASE 2 —Boy aged 10 months was extremely ill with cyanosis a high fever an uncountable pulse and a respiratory rate of 58/minute There was a heavy purpuric rash over the legs and lower

trunk with a few large ecchymoses but no evidence of meningitis Sulfamezathine 0 5 Gm was given intramuscularly and sulfadiazine 0 5 Gm by mouth the latter being continued every four hours At the same time cortisone 25 mg was given every six hours The next day temperature was normal cyanosis had disappeared the pulse was readily perceptible and the color was good No further purpuric spots appeared but neck stiffness became apparent Cortisone therapy was discontinued after a total of 75 mg The infant improved rapidly and convalescence was uneventful

[Evidence is accumulating that cortisone therapy in acute bacterial infections of man may at times be lifesaving We need more experience in this matter See also the next two articles —Ed]

Fulminating Meningococcemia Treated with Cortisone Use of Blood Eosinophil Count as Guide to Prognosis and Treatment According to Horace L Hodes Ralph E Moloshok and Milton Markowitz[1] (New York City) clinical and autopsy findings suggest that acute adrenal insufficiency plays an important role in the production of the Waterhouse Friderichsen syndrome in meningococcemia and is largely responsible for the high mortality in this condition There may or may not be gross adrenal hemorrhage extensive focal necrosis of the adrenal glands has been found without hemorrhage The acute stress of the infection can deplete the adrenal cortical cells of lipid material and this may increase susceptibility to degenerative changes Adrenal cortical extracts have been advocated for the treatment of fulminating meningococcemia although their efficacy was considered dubious

The total blood eosinophil count has been studied as an indicator of the adequacy of the adrenocortical response to the stress of acute infection A low count early in the course of meningococcic infection would indicate an adequate adrenal response on the other hand a normal range in the face of severe infection might indicate a lack of adequate adrenal function The eosinophil count in seven of eight patients with mild or moderate meningococcic infection was low The blood eosinophil count in six patients was 0/cu mm in six patients the initial count in the seventh was 25/cu mm The number of eosinophils rose toward normal values during convalescence The eighth patient was obviously convalescent on hospitalization and his blood contained 100 eosinophils/cu mm When he was given 10 mg ACTH eosinophil count declined

(1) P d tr 10 138 149 August 1952

sharply within six hours None of the patients was critically ill and adrenocortical function as indicated by eosinopenia was adequate All patients recovered

In three patients with fulminating meningococcic infection initial circulating eosinophil count was 75/cu mm in one and 130/cu mm in the others On clinical grounds these patients fell into the Waterhouse Friderichsen category The absence of eosinopenia was considered evidence of poor adrenocortical response Cortisone was added to usual forms of therapy for their treatment One patient died shortly after hospitalization the other two survived Cortisone was believed of value in the two who lived Cortisone may prove of value in the treatment of fulminating meningococcic infection because it is much more potent in overcoming stress than previously used adrenal extracts which had very little cortisone like activity The dose of cortisone used in the treatment of these patients contains the equivalent of about 4 L of aqueous adrenal extract

The dose of cortisone necessary for the treatment of fulminating meningococcemia has not as yet been determined In one patient the initial dose included 100 mg cortisone orally and intramuscularly The oral medication was vomited After 1½ hours 100 mg cortisone was given intravenously An additional 100 mg was given during the ensuing 24 hours This dose may have been excessive for there was fluid retention and evidence of cardiac failure that responded to mercurial diuretics and digitalization

The circulating eosinophil count may be of value as a guide in the prognosis and treatment of meningococcic infections

Cortisone as Adjunct to Chloramphenicol in Treatment of Rocky Mountain Spotted Fever The reported effectiveness of adrenal cortical hormones in ameliorating the toxemia of certain bacterial diseases prompted Joseph B Workman John A Hightower Francis J Borges J Earle Furman and Robert T Parker (Univ of Maryland) to try cortisone combined with chloramphenicol in nine unselected patients with Rocky Mountain spotted fever All were males and five were under age 15 Chloramphenicol in 250 mg capsules was administered orally in a total daily dose of about 50 mg/kg body weight Adults received 3 Gm initially and 1 Gm every 8 hours until afebrile

(2) New E gl d J M d 246 962 966 J 19 1952

for at least 48 hours and children received two thirds the adult dose Cortisone in 25 mg tablets was dispensed orally to three patients and cortisone acetate suspension (25 mg/cc) was given intramuscularly to six Adults received an initial dose of 200 mg followed by two doses of 100 mg each at six hour intervals Children were given two thirds the adult dose Total duration of cortisone therapy did not exceed 12 hours

Clinical improvement was uniformly observed within 24 hours or less of instituting combined therapy The most striking observations were alleviation of headache dissipation of the toxic state and return of appetite There were no deaths The mean duration of fever after institution of therapy was 1 8 days In comparison with treatment by other means the combination of medications significantly enhances amelioration of the signs and symptoms of the disease

Routine use of cortisone in Rocky Mountain spotted fever is not advised but administration of chloramphenicol is vital to the therapeutic regimen The exact role of cortisone in the disease must await the experience with a large number of patients particularly those in the later stages of the disease

ACTH in Reiter s Syndrome Four Cases with Review of Literature are presented by Erling Larson and Samuel J Zoeckler[3] (V A Hosp Des Moines Ia) Although no definite etiology has been established for this self limited triad of acute arthritis urethritis and conjunctivitis it appears that the pleuropneumonia like or L organisms bear a more than casual relationship to this syndrome The classic triad was associated with weight loss and muscular atrophy in four cases Salicylates penicillin streptomycin chloramphenicol terramycin aureomycin sulfadiazine typhoid paratyphoid vaccine and antihistamines were used in one or more cases and failed to influence the course of the disease

Since this is a self limited syndrome the primary objectives of treatment should be shortening the illness and preventing debility and joint contractures This may be accomplished by use of a nutritious diet vitamin supplementation and a vigorous physical therapy regimen The joint pain with its attendant splinting has not been easily overcome in severe cases

ACTH produced prompt and dramatic relief from pain in

(3) Am J M d 14 307 317 M ch 1953

all four patients Appetite was stimulated and vigorous physical therapy measures were possible ACTH contributed greatly to prevention of joint contractures and has a definite place in the over all management of Reiter s syndrome

[Self limited acute inflammatory disorders such as Reiter s syndrome and erythema multiforme seem ideally suited to ACTH or cortisone therapy —Ed]

Corticotrophin and Cortisone Treatment for Systemic Lupus Erythematosus Edmund L Dubois Robert R Commons Paul Starr Charles S Stein Jr and Robert Morrison[4] (Univ of Southern California) report a study on 79 patients with systemic lupus erythematosus 45 of whom were treated with ACTH or cortisone Diagnosis was confirmed by typical rash L E cells or typical pathologic tissue conditions A geometric mean of life expectancy has been increased by therapy from 22 to 27 months

The amount of hormone therapy to be used can be judged only by the clinical effects Suppression of fever may be a guide during the early stages of treatment Some patients have had dramatic and lasting remissions when given as little as 5 mg ACTH intramuscularly every 6 hours for 10 days In others large doses failed to induce remissions It is the aim of treatment to produce Cushing s state as quickly as possible for it is only when clinical hyperadrenocorticism is induced that the disease is maximally suppressed The most effective way to produce Cushing s state is by the use of large intravenously administered doses of ACTH such as 40 60 mg /day or more If fever persists after 48 hours 100 mg /day may be used As much as 600 mg ACTH daily has been given safely by the intravenous route If the ACTH is placed in 2 5% glucose with 10 mg heparin/L dripping at 10 drops/minute the intravenous drip may run as long as nine days before it is necessary to change the site of administration When veins are not available intramuscular drip may be used Pain can often be alleviated by a preliminary injection of 1 cc (150 250 units) hyaluronidase

When a clearcut state of hyperadrenocorticism is reached the treatment may be changed from continuous to intermittent injection of approximately 20 mg every six hours to maintain the cushingoid appearance The patient must be carefully watched at this point for signs of relapse To date no patient

(4) J A M A 149 995 100 J ly 12 1952

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(3) Am J Med 14 303 317 M b 1953

were still living 8 of them continued treatment and may be maintained in a state of remission indefinitely

[The initial response to steroid therapy is usually excellent but kidney function may continue to deteriorate or the patient may succumb to a fulminating pyogenic pneumonia (pneumococcic staphylococcic streptococcic) —Ed]

STAPHYLOCOCCIC INFECTIONS

Superficial Staphylococcic Infection F C O Valentine (Univ of London) and S P Hall Smith[6] (London Hosp) stress that in furunculosis and sycosis barbae staphylococci are commonly carried from a lesion to infect the skin elsewhere From the earliest stage of a boil to healing virulent staphylococci can be isolated from the overlying and surrounding skin and the bacteria can be carried to other parts of the body including nose eyes external auditory meatus and axillae Dolman was the first to note that in chronic furunculosis the anterior nares are often infected with Staphylococcus pyogenes The rate of carriage in the general population is between 22 and 47%

In 53 cases of furunculosis there was a heavy infection of the nares in 34 light infection in 9 and no infection in 10 In 38 cases the nares infection was penicillin sensitive Of 36 cases of sycosis barbae there was a heavy nasal infection in 27 light infection in 6 and no infection in 3 In 15 cases the nares infection was penicillin sensitive

The plan of treatment was to explain carefully to all patients that the infection was due to minute living organisms in the discharge which could readily be carried to other parts of the body by the fingers and often settled in the nose Cultures were taken of the skin lesions and the nares Cetrimide 1% was used to cleanse the skin around the lesions at each dressing and 3% terramycin ointment was applied to the lesions and the nares twice daily Treatment was continued for four weeks

Follow up studies were possible in 31 cases of furunculosis and 24 cases of sycosis Clinical results were good provided infection was eradicated from the site of carriage the nares In 10 cases of furunculosis with heavy nasal infection that be

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in whom Cushing s state has been induced and maintained has died Adjuvant measures include a 200 mg sodium diet before and during therapy *if the patient does not have a salt losing* nephropathy Potassium chloride 8 12 Gm daily and 500 mg vitamin C daily are given Large doses of testosterone propionate as much as 500 mg daily for 35 days did not virilize seven women with active disease it is given to combat the catabolic effects of steroid therapy

With proper therapy the fever abates in 48 hours joint pains disappear *in several days pleural effusions* and cutaneous lesions subside in one to two weeks L E cells disappeared *within six weeks in seven patients Of the 14 patients in whom* clearcut remissions were induced 5 had mild early nephropathy which cleared completely in all but recurred in 2 Failure to respond usually results from inadequate dosage of the hormones No ill effects such as osteoporosis psychosis or perforated ulcers have been noted after long term cortisone therapy however three patients had spontaneous thrombophlebitis

[These results seem unusually good The authors advocate use of doses larger than most of us employ yet the paucity of untoward effects noted is remarkable —Ed]

Corticotrophin and Cortisone in Acute Disseminated Lupus Erythematosus Results of Long Term Use Louis J Soffer and Richard Bader[5] (Mount Sinai Hosp New York City) report a 3 20 month follow up of 18 patients with lupus erythematosus The high incidence in males (33%) is probably due to diagnostic use of the L E cell phenomenon and less emphasis on the rash which occurred in only 11 patients Fever arthritis L E cells and microscopic hematuria were *found in all cases Treatment with corticotrophin* or cortisone in adequate doses caused prompt remission of fever arthritis pleuritis pericarditis *Raynaud s phenomenon and organic* mental syndrome The rash mucous membrane lesions retinal lesions and serous *effusions cleared more slowly Anemia im*proved slowly in the patients with minimal or no renal damage L E cells persisted despite a *remission in the disease* although at times they disappeared temporarily Renal damage *tended to persist The persistence of azotemia is a serious prog*nostic sign No actual cures resulted Twelve of the 18 patients

(5) J.A M A 149 100 10 8 J ly 12 195

were still living 8 of them continued treatment and may be maintained in a state of remission indefinitely

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(6) La t 2 351 354 A g 23 1952

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Although no strain acquired resistance to terramycin two resistant strains were isolated after treatment Sensitization of the skin to terramycin ointment appears rare

[This looks like an important concept i e eradication of the nasal carrier state in the management of a troublesome condition —Ed]

Antibiotic Resistance of Pathogenic Staphylococci Maxwell Finland and Thomas H Haight[7] report results of tests of 500 strains of hemolytic coagulase positive Staphylococcus aureus for sensitivity to nine antibiotics These strains isolated from patients under treatment for various infections at Boston City Hospital from October 1951 to February 1952 represented a wide cross section of the staphylococcus population as it appeared in patients entering or under treatment at the hospital The most striking findings were the great increase in incidence of penicillin resistant strains and the significant increase over previous findings in the proportion of strains resistant to aureomycin and terramycin Only one fourth of the strains were sensitive to penicillin almost all the rest were resistant and only 2 2% were intermediate in sensitivity About two thirds were sensitive to aureomycin almost one fourth were resistant and 9% were intermediate Only a little more than half the strains were sensitive to terramycin nearly one third were resistant and about 15% were intermediate Almost all the strains were intermediate in sensitivity to chloramphenicol Most strains were intermediate in sensitivity to streptomycin 20% were sensitive and 10% were resistant

Sherris and Florey studied strains of staphylococci from different sources and concluded that penicillin sensitive strains produce types of lesions different from those produced by penicillin resistant strains The sensitive staphylococci were associated with acute and closed lesions and with deep seated

(7) A M A Arch I t Med 91 143 158 February 1953

lesions which were either acute or chronic whereas the penicillin resistant strains were obtained primarily from superficial infections and were less often associated with signs of inflammation and suppuration In the present study there was no correlation between the grade of sensitivity of the staphylococci and the source from which they were obtained

All the aureomycin resistant strains were also resistant to penicillin The same relation existed between penicillin and terramycin The greater proportion of the penicillin resistant strains were either sensitive or intermediate in susceptibility to aureomycin or terramycin also the strains which were sensitive to aureomycin or terramycin included about twice as many penicillin resistant as penicillin sensitive strains The correlation between sensitivity and resistance to aureomycin and to terramycin was very close and might perhaps have been even closer had it not been for the fact that aureomycin had an appreciably greater inhibitory effect than terramycin on many of the strains The close relation between aureomycin and terramycin is consistent with their similar chemical structures

Previou treatment with antibiotics may be of great importance in establishing strains of staphylococci resistant to the antibiotics used Some strains are either naturally resistant to one or more antibiotics or acquire such resistance by exposures in other hosts Although previous antibiotic therapy of any given patient may be an important factor in the occurrence of strains resistant to that antibiotic the widespread use of antibiotics may be of equal or greater importance in the increase in incidence of staphylococci which are resistant to those antibiotics such strains may become or remain pathogenic and retain their resistance when they are disseminated and acquired by patients who have themselves not received such antibiotics This view is supported by the fact that there has been an increase in the proportion only of strains of staphylococci resistant to antibiotics which are widely used and only in places where they are used frequently

[In th s and in the succeeding a ticle evidence is presented to indicate that staphylococcic infect ons are becom ng increasingly d fficult to control w th antib ot c th rapy —Ld.]

Some Observations on Staphylococci and Their Resistance to Antibiotics are presented by G B Leyton[8] (Winnipeg

(8) C d M A J 67 20 2 J ly 195

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(8) C n d M A J 67 202 J ly 195

Manitoba) Penicillin resistant strains of staphylococci presented a major problem in Manitoba as early as 1948 For this reason it became customary to treat most staphylococcic infections with aureomycin early in 1949 At this time breast abscesses and pyoderma of the newborn were extremely common and aureomycin was widely used In addition it was given prophylactically to every newborn baby in certain hospitals This wide usage gave the staphylococci a good chance to show their adaptability From early 1949 most staphylococci isolated in Manitoba were sent to the Provincial Laboratory for phage typing and to test their sensitivity to

PERCENTAGE OF STAPHYLOCOCCUS SPECIMENS SENSITIVE TO PENICILLIN AND AUREOMYCIN

YEAR	NO OF SPECIMENS	SENSITIVE TO PENICILLIN %	SENSITIVE TO AUREOMYCIN %
1949	1 455	50	99
1950	1 424	47	77
1951	1 710	39	72

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This investigation suggests that it is likely that no matter how many antibiotics are produced resistant strains of staphylococci will appear and that every effort should be made to cut down the spread of resistant organisms It appears unlikely however that a race of staphylococci will develop that will be resistant to all therapeutic agents at high concentrations By selecting with care cases for antibiotic therapy it should be possible to keep resistant strains at a low enough level so that when a serious infection occurs the physician has a weapon to use If antibiotics are given indiscriminately as prophylaxis and are used when they are not really necessary while their limitations are not understood an ever increasing

number of resistant strains may appear and be spread by the hospital staff throughout most hospitals and more slowly through the population in general

Micrococcic (Staphylococcic) Enteritis as Complication of Antibiotic Therapy Its Response to Erythromycin William H Dearing and Fordyce R Heilman[9] present additional evidence of resistant strains of Micrococcus pyogenes which developed in 44 patients after the administration of terramycin or aureomycin These organisms when present in large numbers in the intestinal tract may produce varying degrees of gastrointestinal and systemic reactions Such reactions may be extremely severe in patients who are already ill from some disease e g pneumonia or peritonitis or who have had a major operation Erythromycin can eliminate such resistant strains of micrococci from the intestinal tract and alleviate gastrointestinal or systemic reactions

Apparently micrococcic enteritis results from toxins produced by M pyogenes growing in great numbers in the intestinal tract Normally this micro organism is rarely found in the feces and is never seen in large numbers They occur in large numbers only when the normal bacterial flora of the intestine are killed off by antibiotics Many patients harbored resistant strains of M pyogenes in their throats this suggests that antibiotic resistant organisms are transferred from one patient to another in the hospital

Among the enterotoxic reactions were diarrhea with copious greenish stools excessive fatigue and exhaustion fever anorexia nausea vomiting and abdominal distention Varying degrees of shock may appear Some patients exhibit intermittent restlessness and mental confusion It was found that 300-400 mg erythromycin four times a day by mouth eliminated resistant strains from the intestinal tract and promptly alleviated gastrointestinal or systemic reactions

Antibiotic agents should be used only when they are specifically indicated and should not be used promiscuously for the treatment of minor illnesses Use of aureomycin and terramycin is not contraindicated in patients who have diseases which respond to these antibiotic agents

[Erythromycin (trade names include ilotycin and erythrocin) will be valuable indeed if it can control some of the severe staphylococcic enteritids which complicate therapy with aureomycin or terramycin —Ed]

(9) P oc Staff M t May Cl n. 8 1 1134 M 11 1953

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rhagic glomerulonephritis has been less definite The suscep tibility to rheumatic fever does not appear to decrease with age at least during the first three decades Rheumatic fever follows streptococcic infection without apparent regard for the type specificity of the infecting streptococcus

Annual variations have been noted in the occurrence of acute hemorrhagic glomerulonephritis On review of the data from 16 cases of nephritis in Cleveland it was noted that type 12 streptococci were the cause of the preceding infection in 14 instances type 4 in 2 instances Recently in a recruit training camp more than 100 cases of nephritis occurred The type 12 streptococcus was the predominant organism in that outbreak

It therefore seems that the epidemiology of acute hemor rhagic nephritis is basically the epidemiology of certain strains of group A streptococci that are nephrotogenic

[The discovery that only certain types of hemolytic streptococci are likely to cause subsequent development of nephritis is important and clears up some of the apparent inconsistencies which had clouded our concepts of the pathogenesis of rheumatic fever and nephritis —Ed]

Prophylaxis against Group A Streptococcic Infections in Rheumatic Fever Patients Use of New Repository Penicillin Preparation According to Gene H Stollerman and Jerome H Rusoff (New York Univ) rheumatic fever or its complica tions may be prevented by vigorous treatment of the initial streptococcic infection with one of the antibiotics or continu ous antibiotic therapy in rheumatic patients Continuous peni cillin prophylaxis involves relatively large doses orally one to three times a day in the fasting state Parenteral adminis tration of available repository procaine penicillin has not been used for continuous prophylaxis because so many injections would be required A repository penicillin compound has been synthesized that provides detectable blood levels of penicillin in man for prolonged periods after a single intramuscular in jection thereby allowing both economical and practical par enteral therapy

Altogether 1 753 intramuscular injections of N N diben zylethylenediamine dipenicillin G (bicillin®) were given in 10 months to 135 children and 8 adults who had rheumatic fever as prophylaxis against group A streptococcic infection The patients had active rheumatic fever or were convalescing from

( ) J A M A 150 1571 1575 D 0 195

Epidemiology of Streptococcic Infections and Their Nonsuppurative Complications John H Dingle Charles H Rammelkamp Jr (Western Reserve Univ) and Lewis W Wannamaker[1] (Univ of Minnesota) point out that man is the only known natural reservoir of group A streptococci With few exceptions the habitat of the streptococcus is the upper respiratory tract There is some evidence that the organisms are first found in the anterior nares If local factors are favorable the streptococci multiply and spread so that large numbers are found in the nose throat and probably the accessory sinuses In such circumstances clinical illness usually occurs but as acute symptoms subside the number of streptococci in the nose rapidly decreases and after two or three weeks few persons harbor the organisms in the anterior nares Likewise the number of streptococci in the throat decreases but here the organism may persist for months Of 53 patients in the convalescent phase of untreated acute tonsillitis and pharyngitis due to group A streptococci 90% still harbored the organism in their throats at the end of three months

There are two concepts as to the routes of transfer of organisms from the initial carrier to the recipient (1) directly between the two persons through physical contact or by droplets passing through the air for short distances and (2) indirectly through fomites or via the air by means of droplet nuclei and dust There is little if any direct evidence indicating the relative importance of these modes of spread or even whether any of them is epidemiologically important Repeated attempts to control the environment with ultraviolet light aerosols and the oiling of floors and blankets have had little effect on the spread of hemolytic streptococci or of other organisms causing respiratory disease The most tenable hypothesis is that intimate contact such as occurs in the home and school is required for effective spread of disease

There is a temporal and probably causal relation between group A streptococcus infections and rheumatic fever The relation between streptococcic infection and acute hemor

(1) Lancet 1 736 738 Apr 11 1953

Treatment of Pneumococcic Meningitis Since the Introduction of Penicillin Count Dillon Gibson and D Geraint James[3] *report results with penicillin in* 31 unselected cases of proved pneumococcic meningitis seen at the Presbyterian Hospital New York City between 1944 and 1950 Half the patients were under 2 and the rest over 20 Penicillin was given intrathecally as well as intramuscularly to all but one patient Three died within 24 hours of the start of treatment The respiratory tract harbored the infecting organism in 16 patients Half of the isolated pneumococci belonged to the first eight *serologic types Blood cultures in 27 patients recovered* a pneumococcus of the same type as in the cerebrospinal fluid

In 28 who recovered temperatures returned to normal on about the eighth hospital day This figure did not change during the years despite the *increasing dose of penicillin*

During 1944 50 the intramuscular dosage of penicillin climbed steadily from an average 200 000 units daily in 1944 45 to 1 600 000 units daily in 1950 The average length of treatment remained 15 days throughout Penicillin intrathecally was given for an *average of seven days with daily* injections of 15 000 50 000 (usually about 25 000) units The intrathecal dosage remained steady throughout the years Infants tolerated 50 000 units of penicillin intrathecally with no *ill effects and without residual neurologic lesions*

The dangers of penicillin intrathecally have been overemphasized Early sterilization of the cerebrospinal fluid outweighs any doubtful complications due to penicillin The *crystalline preparations of today need give no anxiety to the* clinician compared with anxieties over the undertreated patient

Results with penicillin intramuscularly have not surpassed *those obtained in this series* Damage to the central nervous system from intrathecal medication has not been observed Given intrathecally penicillin can exert a beneficial effect on meningitis The recommended intramuscular dosage is 2 000 000-4 000 000 *units daily for two weeks* intrathecally

(3) La 1 2 1203 1205 Dec 8 1952

a recent attack One of the following dose schedules was used 300 000 units intramuscularly once weekly 600 000 units once every two weeks or 1 200 000 units once a month In 10 patients who received 1 200 000 units of bicillin® intramuscularly in divided doses of 600 000 units given simultaneously in each buttock all had detectable serum levels after one week 89% after two and three weeks and 67% after four weeks

Routine weekly throat cultures were negative for group A streptococci in all but one patient The pharyngeal flora in patients receiving regular injections did not noticeably change The usual saprophytic gram positive and gram negative organisms were as common before and during penicillin prophylaxis Incidence of monilia in throats or stools of 77 patients did not increase The penicillin resistance of 27 strains of Streptococcus viridans isolated from the pharynx in 27 patients treated regularly for six months or more was evaluated to establish any threat of subacute bacterial endocarditis that would not be amenable to penicillin therapy Their penicillin resistance was well within the range of in vitro sensitivity of strains encountered in subacute bacterial endocarditis that ordinarily respond to penicillin Nonhemolytic streptococci isolated from patients on bicillin® were slightly less resistant than those isolated from patients on penicillin orally but were somewhat more resistant than those isolated from a control group Subacute bacterial endocarditis did not appear after 77 dental extractions performed in 38 patients receiving bicillin®

Intramuscular injection usually caused moderate burning and discomfort for several minutes After several hours deep muscle soreness was often felt for 24 hours This reaction was rarely severe enough to limit activity Penicillin hypersensitivity was encountered in four patients Urticaria in one patient and a papular rash in another subsided in 6 and 72 hours and did not reappear despite further penicillin therapy

The study indicates that bicillin® can produce serum levels of penicillin for a prolonged period and that the streptococcus carrier state can usually be eliminated

[This preparation appears to be the ideal penicillin for treatment of streptococcic infections of the upper respiratory tract The important factor for prevention of rheumatic fever or nephritis is prolonged therapy with penicillin and that can be achieved in adequate levels for the very sensitive hemolytic streptococcus by giving a single injection of bicillin® —Ed]

therapy were extremely ill and that may account for the poor results

It is concluded that penicillin in large doses is a satisfactory therapeutic agent that can be used in lieu of sulfonamides for the average patient with meningococcic meningitis

[We have continued to employ sulfonamides for meningococcic infections because of early observation that some strains were moderately resistant to penicillin Apparently however that resistance can be overcome by massive doses of penicillin such as are advocated *here* This regimen has *one* big advantage at the beginning of therapy it may be impossible to determine the etiology of a pyogenic meningitis this dosage of penicillin would suffice for either one of the common causes of meningitis in adult —pneumococcus or meningococcus —Ed]

Treatment of Meningitis with Chloromycetin® Palmitate Results of Therapy in 23 Cases are reported by Garrett E Deane J Earle Furman Alice R Bentz and Theodore E Woodward[5] (Univ of Maryland) Chloromycetin® palmitate is a palatable liquid preparation of chloramphenicol in which one of the hydroxyl groups of the propanediol chain has been replaced by an ester group

In 23 patients with pyogenic meningitis therapy was begun as soon as purulent cerebrospinal fluid was detected Chloramphenicol hydrochloride was given intravenously in dosage of 50 mg /kg body weight to patients who were vomiting or comatose As long as the patient's clinical condition necessitated intravenous therapy he received intravenous drug in divided six hourly doses calculated on the basis of 50 mg /kg /day The total intravenous dose varied from 0 25 to 3 2 Gm and averaged 1 3 Gm After intravenous medication chloromycetin® palmitate was given in dosage of 150 mg /kg /day in 19 cases and 100 mg /kg day in 4 Eleven patients received chloromycetin® palmitate alone

Hemophilus influenzae meningitis type B was present in *12 patients and in 11 the cerebrospinal fluid was sterile on an average of 33 6 hours after therapy began 1 patient died All of eight patients with Neisseria intracellularis meningitis had* sterile cerebrospinal fluid *on an* average of *27 4 hours after* therapy began Three patients with meningitis due to types 29 18 and 12 Diplococcus pneumoniae had sterile fluid after three days of therapy

There was complete recovery in 22 patients Temperatures returned to normal within 2 1 days after treatment began All

(5) P d 11 368 380 Ap 1 1953

doses do not exceed 25 000 units dissolved in 10 ml physiologic saline solution given daily until definite improvement is noted

[Remarkably good results —Ed]

Meningococcic Meningitis Treatment with Large Doses of Penicillin Compared to Treatment with Gantrisin® Mark H Lepper Harry F Dowling Paul F Wehrle Normal H Blatt Harold W Spies and Michael Brown[4] (Univ of Illinois) have re evaluated the effect of penicillin in meningococcic meningitis for its possible use in patients hypersensitive to sulfonamides and in patients in whom pneumonococcic meningitis and meningococcic meningitis have not been definitely differentiated In an alternate case study 40 patients with meningococcic meningitis were treated with 1 000 000 units of sodium or potassium penicillin every two hours intramuscularly 38 others were given 0 05 0 06 Gm gantrisin®/lb body weight intravenously initially and 0 1 0 13 Gm /lb every 24 hours thereafter either by mouth or parenterally If the patient receiving penicillin did well after 24 48 hours 600 000 units of procaine penicillin in aqueous suspension was substituted for every third dose of penicillin for the next 24 hours if the course was still favorable the soluble salt was discontinued and injections of procaine penicillin suspension were continued at six hour intervals In infants procaine penicillin dosage was decreased to 600 000 units every 12 hours on the fifth day Aureomycin was combined with penicillin in 11 cases because of the nature of previous treatment or uncertainty of diagnosis Penicillin was combined with gantrisin® in 14 cases A combination of various antibiotics was used in 27 cases

Of 130 patients treated 11 died The rate of recovery in the different therapeutic groups was about the same Penicillin was at least as effective as gantrisin® possibly more so in the treatment of meningococcic infection Gantrisin® can accomplish everything that is expected of sulfadiazine but has the advantage of causing no renal complications Results were poor when penicillin and gantrisin® were combined in fulminating infections

Addition of adrenal hormones and blood products to the chemotherapeutic agents used in fulminating infections did not improve results The patients who received this added

(4) J Lab & Clin Med 40 891 900 D ec 195

the most striking observation initially is the density of the shadow which is usually homogeneous and may be suggestive of fluid There may be bulging and sagging of the interlobar septa

The condition does not respond to penicillin Before the introduction of antibiotics mortality was about 80% Streptomycin has reduced the death rate but the prognosis remains serious as about a third of the cases recorded in the literature were fatal despite antibiotic therapy Only one of the authors six patients died Two were left with multiple small thin walled lung cavities but they were able to return to work

Intrabronchial Use of Streptokinase and Streptodornase in Treatment of Slowly Resolving Pneumonia According to Joseph M Miller John A Surmonte and Perrin H Long[7] (Fort Howard Md) healing of the parenchyma of the lung depends not only on phagocytic action but also on removal of exudate from the alveoli and terminal bronchioles to permit re expansion of involved segments The exudate is composed of fibrin desoxyribonucleoprotein desoxyribose nucleic acid living and dead leukocytes and desquamated bronchial epithelium The enzymes streptokinase and streptodornase can digest the exudate The chief problem in the enzymatic treatment of infections in the parenchyma of the lung is the difficulty of establishing and maintaining contact between the enzymes and exudate

Two patients with slowly resolving pneumonia were treated by the intrabronchial administration of streptokinase and streptodornase After routine diagnostic bronchoscopy the patient was so positioned that the diseased pulmonary tissue was dependent A catheter was placed through the bronchoscope and the enzymes injected The bronchoscope and catheter were withdrawn and the patient instructed to maintain the position for four hours if possible Subsequent therapy was given through a catheter passed into the bronchial tree Postural drainage with the affected area uppermost was performed four times a day The results in both patients were excellent

Bronchoscopic examination should always precede the use of streptokinase and streptodornase to enable detection of a bronchogenic carcinoma which could cause the infiltration and

(7) Dis Chest 23 149 153 February 1953

patients were able to take the chloromycetin® palmitate orally after the first 24 hours despite the original severity of their illness

Chloramphenicol has been effective against all types of pyogenic meningitis It can be supplemented by penicillin if a pneumococcic infection is present A dosage of 150 mg /kg / day of orally administered chloromycetin® palmitate will give effective blood and cerebrospinal fluid levels

No adverse blood reactions attributable to chloramphenicol were observed in over 600 patients ill with various acute infectious diseases Chloramphenicol is a valuable antibiotic for the treatment of specific acute infectious diseases but not for minor poorly defined illnesses Its promiscuous use is unwarranted

[In children of course H influenzae is an important cause of pyogenic meningitis for which even massive doses of penicillin would not be effective chloramphenicol therefore is perhaps the best all around agent for meningitis in children under age 8 —Ed]

PNEUMONIA AND EMPYEMA

Friedlander's Pneumonia J M Barber and A P Grant[6] (*City Hosp Belfast*) report six cases which represented 2 5% of all pneumonia cases in the hospital The disease occurs mostly in elderly persons and is rare in childhood The ratio of males to females is about 6 1 All six cases occurred in males Onset is usually acute with rigors pleural pain and cough Signs of pulmonary consolidation are similar to those in other types of pneumonia Often more than one lobe is affected the upper lobes being particularly vulnerable Temperature is rarely high About 25% of patients have a characteristic sputum consisting of a sticky homogeneous emulsion of blood and mucus There may be rapid destruction of the lung stroma with cavitation occurring within a few days The thin walled cavities must be differentiated from tuberculous cavities especially as they often involve the subapical regions The cavities may be multiple The patients are usually symptomless and the condition may remain stationary for years

The radiologic picture of acute Friedlander s pneumonia may resemble that of ordinary pneumonic consolidation but

(6) B r M J 752 755 Oct 4 19 2

(Morrisania City Hosp New York City) state that in a significant group of cases bacterial endocarditis is caused by unusual organisms or unresponsive strains against which penicillin therapy is ineffective This has led to the use of some of the new antibiotics in combination with penicillin In some instances as many as three or more antibiotics have been used together with favorable results after treatment with penicillin alone has been futile The authors report a case of subacute bacterial endocarditis in which bacitracin alone was used They were unable to find a similar report in the literature

Man 49 who had rheumatic heart disease in congestive heart failure with subacute bacterial endocarditis was treated with penicillin in large dose streptomycin and terramycin without improvement Blood cultures revealed growth of a diphtheroid bacillus which was sensitive to bacitracin The patient was given 60 000 units of bacitracin intramuscularly daily in divided dose of 20 000 units every eight hours Therapy was continued for 31 days for a total of 1,860 000 units The drug was well tolerated The only abnormal findings were the presence of albumin coarse and fine granular cast and occasional red blood cell in the urine which persisted only during the first two weeks of therapy After completion of therapy the urinary findings disappeared The patient recovered from the subacute bacterial endocarditis is asymptomatic and has a negative blood culture

Meleney has given similar and even larger amounts of bacitracin over longer periods without any serious reactions He feels that with the use of the less toxic drug now being manufactured if the dose is limited to a maximum of 80 000 100 000 units daily evidence of kidney damage will be minimal and always reversible

Streptococcus Viridans Subacute Bacterial Endocarditis Two Week Treatment Schedule with Penicillin When subacute bacterial endocarditis was first treated with penicillin eight years ago clinicians quickly learned that with the small amounts used relapse could be averted only by continuing therapy for many weeks The chance observation in 1946 that a patient who did not respond to conventional doses of penicillin given for many weeks was cured in 11 days with a daily dose of 15 000 000 units led Morton Hamburger and Leon Stein[1] (Cincinnati) to make a systematic study of the possibility of reducing the treatment period in other patients Crystalline sodium penicillin G was given to 12 patients with subacute bacterial endocarditis caused by penicillin sensitive

(1) J A M A 149 542 545 J 7 195

atelectasis The mechanical removal of purulent exudate by aspiration at bronchoscopy is a definite although sometimes temporary help in the treatment of the atelectasis that accompanies the unresolved pneumonia The intrabronchial instillation of streptokinase and streptodornase is contraindicated in active pulmonary tuberculosis to avoid possible bronchogenic spread of the disease All examinations possible to eliminate the presence of tuberculosis should be done before treatment is started

Treatment of Nontuberculous Bacterial Pleural Space Infections with Aureomycin Results of Treatment in Nine Patients Concentration of Aureomycin in Pleural and Pericardial Fluid in Seven Patients Charles K Wolfe Jr Mark H Lepper Eston R Caldwell Jr Harold W Spies and Harry F Dowling[8] (Georgetown Univ) point out two features of the pleural cavity that contribute to the difficulty of curing infections in this area First the ability of different drugs to pass into the pleural space is variable and second the resorption of proteinaceous material from the pleural space is minimal even when the process is sterile In nine patients with nontuberculous bacterial empyema aureomycin (250 500 mg every three hours) was used in combination with repeated aspirations when necessary

Aureomycin possesses the advantage over penicillin and streptomycin of having a broader antibiotic spectrum and diffusing readily across the pleural space as demonstrated by the concentration of the antibiotic in the pleural fluid Aureomycin alone cured two patients with infections caused by a pneumococcus and a beta hemolytic streptococcus In five others the importance of removing the pleural fluid even though the antibiotic penetrates in adequate concentration was illustrated It appeared that aureomycin combined with adequate drainage was superior to penicillin Drainage may be accomplished by repeated aspirations with or without proteolytic enzymes as indicated or by thoracotomy

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BACTERIAL ENDOCARDITIS

Diphtheroid Subacute Bacterial Endocarditis Successfully Treated with Bacitracin. Joshua F Zendel and Alfred Lubart[9]

(8) Ann I t Med 37 164 171 July 195
(9) A M A A ch I t M d 90 56 568 O t be 1952

bacterial endocarditis In 3 15% of cases the causative agent is an enterococcus and a combination of penicillin and streptomycin is necessary

Results of clinical and in vitro investigations have led to the current tendency to use combined treatment for bacterial endocarditis Penicillin with streptomycin penicillin with bacitracin and terramycin with streptomycin have been used when the causative organism has been found resistant to commonly used antibiotics given alone

Joseph E Geraci (Mayo Clinic) reviews experience with treatment of 46 patients with subacute bacterial endocarditis Streptococci were isolated in 34 Of 32 strains of streptococci tested 59% were penicillin sensitive Penicillin alone was used in 9 patients and combined therapy in 37 In 30 of the 34 cases of streptococcic endocarditis therapy consisted of penicillin with dihydrostreptomycin One patient with endocarditis caused by hemophilus was given terramycin and dihydrostreptomycin for two weeks and fully recovered Mortality rate of the series was 24% Deaths were caused by congestive heart failure cerebral embolism renal insufficiency and pulmonary embolism

For 15 patients in whom endocarditis was caused by penicillin sensitive streptococci combined short term therapy with penicillin and dihydrostreptomycin was used Daily dose varied between 1 200 000 and 2 400 000 units of penicillin and between 1 2 and 2 4 Gm dihydrostreptomycin For 13 patients treatment continued for 14 days for 2 patients 20 days Response was good and prompt Temperature fell to normal either on the day treatment was started or the day after Four of these patients died three of congestive cardiac failure and one of cerebral embolism Total number of cases is small and more experience is needed before final conclusion can be drawn but combined therapy seems practical and curative in endocarditis caused by penicillin sensitive streptococci

Seven patients with endocarditis due to an enterococcus were treated with combined therapy Daily dose of penicillin varied from 6 000 000 to 15 000 000 units given by continuous intravenous drip for 28 50 days Dihydrostreptomycin in doses of 0 5 Gm was given intramuscularly every six hours for the first two weeks then 0 5 Gm twice daily Six of the seven

(2) M M 35 861 866 September 19 2

streptococci Treatment was given for two weeks the daily dose being 15 000 000 or 16 000 000 units intravenously to the first few patients and intramuscularly to the others Each dose was administered in a total volume of 5 cc distilled water including 2 cc of 1 2% procaine hydrochloride to alleviate discomfort The penicillin was given in doses of 2 000 000 or 2 500 000 units every three or four hours to those receiving it intramuscularly

Of the 12 patients 10 were living 16 5 55 months after cessation of treatment Two patients died of cardiac failure and pulmonary infarction respectively however autopsy revealed that a bacteriologic cure had been effected Two patients relapsed within a month after treatment and were successfully treated with a second two week course

Studies on the penicillin sensitivity of the streptococci showed the minimal inhibiting concentration of penicillin to be 0 06 units (0 036 μg) or less/cc medium for nine strains two strains required 0 1 unit (0 06 μg) and one strain 0 2 unit (0 12 μg)/cc medium

Of the 10 living patients 7 are in school or are pursuing occupations at which they were employed before their infection Only one requires digitalis One is invalided by hemiplegia one had cerebral and cardiac symptoms of advanced aortic stenosis and one had chronic congestive heart failure

These results show that a two week course of intensive penicillin therapy can achieve bacteriologic cure in subacute bacterial endocarditis Although the 16 7% relapse rate is no lower than that achieved by longer dosage schedules the practical and economic value of a two to six week reduction in hospitalization is obvious

[No doubt many cures can be effected with only two weeks of treatment nevertheless one is tempted to play safe and continue therapy a little longer With enterococcic infections six weeks therapy is recommended See the succeeding article —Ed]

Antibiotic Therapy of Bacterial Endocarditis II Current Trends in Treatment of Subacute Bacterial Endocarditis If endocarditis is caused by organisms sensitive to a concentration of penicillin of 0 1 unit/cc or less the recommended minimal daily dose of penicillin is 2 000 000 units for four to six weeks When the causative organism is more resistant to penicillin daily dose is larger Streptococci sensitive to penicillin have been found to cause 80 90% of cases of subacute

Cold precipitable globulins are also found in kala azar multiple myeloma and polyarteritis nodosa

[There is a good deal of interest currently in cryoglobulins Their occurrence in endocarditis is of unknown significance now Tl t st is simple and might rarely be of value in suggesting consideration of this diagnosis —Ed]

TYPHOID FEVER

Treatment of Typhoid Fever with Chloramphenicol Clinical Study of 330 Cases of Enteric Fever Treated in Egypt. D E Marmion[4] (R A M C) discusses two large outbreaks of typhoid fever in the Suez Canal Zone in the summer of 1950 and the usual few poradic cases of typhoid and paratyphoid fever Laboratory confirmation of the diagnosis was made in all but two ca es All patients received adequate nutrition on a soft diet during the febrile per od a high calorie (3 000/day) low residue diet in early convalescence and a very high protein and calorie diet (4 000 5 000/day) in later convalescence Chloramphenicol dosage ranged from 30 to 38 Gm over a period of 10 14 days The severity of the illness in patients with and without preventive inoculation could not be compared since all patients had been inoculated But so many had disease of the highest severity that it seems unlikely that inoculation could have had any modifying influence

A study of clinical response to chloramphenicol revealed that defervescence usually took three to five days From the start of treatment to the end of defervescence took an average of 2 8 days in mild 3 8 days in moderate and 4 3 days in severe cases average for all ca es was 3 9 days An interval of hypothermia with low blood pressure and a thenia often followed defervescence especially if rapid Toxemia symptoms improved *pari passu* with the fever or a little in advance of it Sometimes headache was relieved within a few hours but usually there was little change in the first 36 48 hours of treatment Abdominal symptoms especially pain and distention were the last to sub ide

Blood cultures almost invariably became s erile within a few hours of starting therapy Salmonella organisms tended to disappear from the feces during therapy but sometimes reappeared after varying intervals Bacteria were not carried

(4) T R y Soc T p M d & Hyg 46 619 638 N embe 195

patients recovered Six weeks of combined therapy appears to be the safest schedule for enterococcic endocarditis Incidence of toxicity from the dosage of dihydrostreptomycin was small

Cold Precipitable Serum Globulins ("Cold Fractions," "Cryoglobulins") in Subacute Bacterial Endocarditis F Dreyfuss and G Librach[3] (Hebrew Univ Hadassah Med School Jerusalem) report observation of spontaneously appearing precipitates in serums most of which—excluding bacterial contamination—tend to occur on standing in the cold (4 11 C) for varying intervals A few reports have described the *occurrence of cold precipitable globulins in various disorders mainly in conditions accompanied by hyperglobulinemia* Large amounts of cold precipitable globulins sometimes produce a cold sensitivity syndrome manifested by purpura progressive anemia Raynaud s phenomenon occasional ulcerations and thrombotic manifestations

Cold precipitable globulins are fairly common in subacute bacterial endocarditis they *were found in 61 6% of 180 serums examined in 50 cases of this disease In only 8 of the 50 patients* was such a globulin not detected at any time during the study

METHOD—Serums to be tested for cold precipitable globulins were promptly separated from the clot to avoid their precipitation with the clot About 1 ml serum was put into a refrigerator An opacity (*traces*) or a precipitation at the bottom of the tube (positive *cold fraction*) *was looked for after 24 48 hours A precipitation which would not dissolve on warming was not considered a* cold precipitable globulin

Clinical bacteriologic or biochemical data did not differ between the group which *exhibited cold precipitable globulins and the group which did not Although disappearance of a cold fraction was noted in some* patients who recovered from the *infection this sequence* could not be demonstrated often enough to make it a valuable prognostic finding

An abnormal globulin pattern in subacute bacterial endocarditis regardless of the micro organism involved seems to represent a facet of particular host response that appears comparatively early in the course of the disease This adds a point to the concept of the disease as a special type of reaction of *a predisposed* host to pathogenic micro organisms of low *virulence*

(3) J Lab & Cl M d 40 489 497 Octob 1952

The literature indicates that relapses are more common after chloramphenicol therapy than among untreated patients That relapses were commoner in patients treated earlier supports the view that curtailing the disease prevents full development of immunity if this is so it emphasizes the need for vaccine therapy or some other expedient to prolong the stimulation of immunity mechanisms

[This report on a large series of cases is of value Experience on such a scale is no longer available in this country The toxic crisis described early in treatment may well be a Herxheimer type of reaction—Ed]

Effect of Interrupted Courses of Chloramphenicol on Relapse Rate in Typhoid Fever Effect of chloramphenicol on the course of typhoid fever is uniformly good but rate of relapse is high (26% of 121 cases in the literature) A T John and V S Vinayagam[5] report the responses of 20 patients with typhoid fever to interrupted courses of chloramphenicol compared with those of 17 having a single continuous course of chloramphenicol In almost all patients treated with single continuous courses relapses occurred if at all between the 9th and 22d day after the patient had become afebrile To prevent relapses instead of continuing administration of chloramphenicol uninterruptedly for so many days after clinical cure it was withdrawn soon after pyrexia had subsided and a second course started just before the earliest time at which a relapse might be expected

As soon as typhoid fever was diagnosed the patient was given 0 25 Gm chloramphenicol every two hours until temperature was normal Thereafter 0 25 Gm chloramphenicol was given every four hours until the patient had been afebrile for 48 hours No chloramphenicol was given in the next five days On the sixth day a further course of chloramphenicol 0 25 Gm every six hours was given for six days

Of 20 patients treated with interrupted courses of chloramphenicol 1 (5%) relapsed Of 17 treated with a single continuous course of chloramphenicol 7 (41%) relapsed Of the 17 12 had chloramphenicol for six days or more after they had become afebrile and 4 (33%) relapsed There was no difference between the two groups regarding age sex general immunity nutrition and source of infection

Average dose of chloramphenicol given the 20 patients treated with interrupted courses was 19 Gm and that for the 17 treated with single continuous courses was 22 Gm It is

(5) Lancet 2 757 759 Oct. 18 1952

longer than 90 days and there were no permanent carriers Agglutination titers varied widely it would have been possible to diagnose typhoid fever on serologic evidence alone only 50% of the time

Nine patients had a toxic crisis manifested by a drug induced exacerbation of toxemia early in treatment The crises were always in severe and extremely severe cases and the clinical picture was as varied as that of the typhoid fever itself The symptoms of typhoid fever itself were aggravated without the appearance of any new or specific features

Toxic effects attributed to chloramphenicol were noted in 44% of 300 typhoid fever cases and 22 6% of 30 cases of paratyphoid fever most common were stomatitis glossitis and pharyngitis Gastrointestinal symptoms (unpleasant taste nausea vomiting and diarrhea) were experienced by some A few patients had urticaria 2 7% had drug fever and although its nature remains obscure its association with urticaria suggests allergic origin

Chloramphenicol reduces but does not eliminate the classic complications of typhoid fever Two patients had gastrointestinal perforation while taking the drug The commonest complication was water and electrolyte deficiency Fluid and salt were lost in sweat vomitus and diarrhea and into the lumen of the bowel in hemorrhage and in the urine This resulted in drowsiness and apathy different in a subtle way from the prostration of typhoid fever and somewhat resembling the lethargic spinelessness of anoxia

Of three deaths (1%) in the typhoid series one was due to circulatory failure in a toxic crisis and one to a perforation one patient was treated too late

Relapse rate was 28% in typhoid and 13 8% in paratyphoid fever Relapses were generally milder than the initial attacks and were treated with increased doses of chloramphenicol and vaccine Second relapses were rare

Although chloramphenicol has proved effective in treatment of enteric fevers its side effects and failure to reduce the incidence of relapses must be considered Clinically defervescence was slower in severe than in mild cases but the stage at which treatment was commenced was not significant The toxic crisis is probably due to release of endotoxin from killed organisms Cortisone in conjunction with chloramphenicol may reduce the severity of the toxic crisis

retained in the spleen or lymph nodes sites of greatest multiplication of brucellas Therefore 80 mg insoluble amphoteric terramycin was injected into deep subcutaneous tissues of patients with brucellar bacteremia at weekly intervals for six to seven weeks No irritation such as that seen with similar injections of soluble terramycin was noted Bacteremia continued for two weeks and symptoms disappeared slowly as compared to prompt suppression of symptoms by 2 Gm terramycin daily by mouth Of 40 patients treated only 22 were followed for more than six months of these only 4 showed clinical and bacteriologic relapse one at four months the others at six months

[The author s rationale for using an insoluble terramycin preparation is interesting but more evidence is needed to establish its real value —Ed]

Oxytetracycline-Streptomycin Therapy in Brucellosis Due to Brucella Melitensis Gordon B Magill and John H Killough[7] (U S Naval Med Res Unit No 3 Cairo) studied the response of 23 patients with acute or subacute brucellosis to treatment with a combination of oxytetracycline (terramycin) and streptomycin in view of the high incidence (69%) of relapses observed in a previous investigation after administration of any one of three antibiotics for an average of 12 days Blood and urine were cultured daily for four days before therapy was initiated Br melitensis was isolated from the blood of 22 patients and also from the urine of 12 Brucella agglutinations in 22 cases ranged from 1 320 to 1 5 120 The one case in which brucella was not recovered was clinically indistinguishable from the others

Terramycin was given orally every four hours and streptomycin or dihydrostreptomycin was given concomitantly once a day intramuscularly Twenty one patients received 3 Gm terramycin daily for the first week and 1 5 Gm daily for the subsequent two weeks In addition these patients received 1 Gm streptomycin daily for three weeks The total doses for each of the 21 patient was 42 Gm terramycin and 21 Gm streptomycin One patient aged 10 was treated with half doses of both antibiotics Therapy for the other patient was varied because of an unusually resistant infection

Clinical response was good and control of acute symptoms adequate The patients became afebrile in three to even days

(7) A M A A h I t M d 91 204 11 F b y 19 3

evident that interrupted courses of chloramphenicol prevent relapse more effectively than do continuous courses The relapse rate is lowest when chloramphenicol is withdrawn soon after clinical cure and given again just before a relapse can be expected

[Both of the preceding papers tress the problem of relapses in chloramphenicol treated typhoid fever I am not convinced that the superiority of interrupted courses of treatment is proved conclusively in the series of cases quoted above but the findings are at least sugg tive —Ed]

BRUCELLOSIS

Treatment of Brucellosis According to M Ruiz Castañeda[6] (Mexico City) the discrepancy of in vivo and in vitro activity of antibiotics against brucella organisms may be due to intra cellular multiplication like that of rickettsias which has been demonstrated in embryo cultures and in some pathologic observations Streptomycin alone or combined with other antibiotics has proved incapable of destroying all intracellular brucella after 24 hours exposure in vitro

In 237 brucellosis patients given only symptomatic treat ment clinical manifestations lasted an average of 60 days but after this interval only 30% had clinical relapses Of 61 patients treated with a streptomycin sulfadiazine combination 67 2% relapsed after the 60th day despite reduction of the initial symptomatic period to an average of 13 6 days Aureo mycin orally limited symptoms to four days but relapses numbered 40% with an aureomycin streptomycin sulfadiazine combination relapses were somewhat less common and with terramycin they numbered 37% (All figures cover only the relapses that occurred more than 60 day after initiation of therapy)

Known antibiotics do not appear to affect the intracellular phase of brucella nor in soluble form to penetrate the cyto plasm of phagocytes although some antibiotics in the insoluble form are phagocytized by polymorphonuclear cells and mono cytes As phagocytes tend to accumulate in irritated areas including foci of infection it is conceivable that phagocytized particles of antibiotics will be transported to areas of infection and that phagocytes aged or altered by the antibiotics are

(6) Gac méd Me o 8 135 14 M Ap 195

brucella cells in their tissues without symptoms and should be considered carriers Healthy appearing animals may harbor and disseminate brucella for years Cattle with and without a history of abortions may shed brucella in milk and udder secretions for months and years Although there is ample evidence that brucella can parasitize the cells of animals without demonstrable ill effect there is little similar information concerning man Brucella organisms have been isolated from the blood of a few patients after recovery from acute brucellosis and at a time when they insisted they had no symptoms It seems reasonable to assume that man as well as animals participates in a host parasite relation with brucella possibly more often than is appreciated but precise evidence is needed to prove this thesis

Several years ago Spink became impressed not so much by the debilitating type of illness caused by brucella as by the absence of localizing complications in most patients They appeared ill and had many complaints yet presented few or no physical abnormalities It seemed likely that these patients were ill because of the widespread dissemination of brucella in the tissues

Relatively few histologic studies on autopsy material were found in the literature Because brucella organisms tend to localize in the reticuloendothelial tissues studies were therefore made of tissues obtained from the sternal bone marrow and liver of ambulatory patients by biopsy technics Granulomatous lesions composed of epithelioid cells giant cells of the Langhans and foreign body types and a cellular infiltrate composed of lymphocytes plasma cell and occasionally eosinophils were seen Disabling complications from localization of the brucella have been observed in several instances The most commonly encountered complication involved the skeletal system especially the spine The second commonest complication is involvement of the peripheral and central nervous system Four cases of encephalomeningitis have been reported Subacute bacterial endocarditis and orchitis have been seen occasionally

Each of the three species of brucella produce different patterns of disease In general infection due to Brucella melitensis results not only in incapacitating and debilitating com

Symptoms such as arthralgia headache and malaise persisted longer than fever requiring an average of about eight days to disappear Blood cultures were still positive 24-48 hours after institution of therapy in seven cases They remained positive in two of these at the fifth day and in one at the seventh day There was no correlation between persistence of bacteremia and either rate of clinical response or tendency to relapse A Herxheimer like reaction occurred in 55% of patients when first given treatment but in none was it severe or prolonged

Of the 22 patients treated for three weeks only 3 (14%) relapsed This is a great improvement over the previous relapse rate One patient had a single temperature elevation to 100 6 F on the eighth post treatment day For the following 10 weeks he remained asymptomatic and then suddenly had a full blown clinical relapse with high fever and positive blood and urine cultures Another patient had a clinical relapse 20 days after treatment but the organism was not isolated despite 24 post treatment cultures Both of these patients were re treated with terramycin plus streptomycin with increased doses of the former (4 5 Gm daily for the first week and then 2 25 Gm daily for the subsequent two weeks) They were observed more than six months after retreatment and showed no evidence of another relapse The third relapse was bacteriologic without clinical signs in a patient who had a positive blood culture four months after therapy This patient was not re treated because subsequent cultures were negative and the patient continued to deny having symptoms

[This seems to be the treatment of choice for brucellosis in the present state of our knowledge —Ed]

Some Biologic and Clinical Problems Related to Intracellular Parasitism in Brucellosis are discussed by Wesley W Spink[8] (Univ of Minnesota) Interest in intracellular parasitism by brucella has stemmed from the following problems (1) the mechanism or mechanisms whereby brucellosis can exist as a chronic infection in animals and in man and (2) failure of antibiotics to eradicate completely brucella from the tissues of some patients and from experimentally or naturally infected animals Both animals and man may harbor viable

(8) New England J Med. 47 603-610 Oct 16 1952

Bacteroides Infections Clinical, Bacteriologic and Therapeutic Features of 14 Cases A Murray Fisher and Victor A McKusick[9] point out that bacteria of the genus Bacteroides have only relatively recently been recognized as important pathogens for man There have been 14 instances of bacteroides infection in the past six years at Johns Hopkins Hospital These bacteria include nonspore forming strictly anaerobic gram negative bacilli They are normal inhabitants of the human body being particularly abundant in the mouth female genital tract and intestinal tract They have been found in putrid gangrenous diseases of many types and are often associated with other anaerobes which are common inhabitants of the mucous membranes The infections are much like those due to the anaerobic streptococcus which is one of the species often found in association with them One feature common to the bacteroides group is that the bacteria are extraordinarily difficult to isolate

Among the 14 cases there were 2 of subacute bacterial endocarditis due to bacteroides superimposed on previously unrecognized rheumatic heart disease In one case lung abscess empyema and bronchopleural fistula in an epileptic probably resulted from aspiration of bacteroides from the tonsillar area Toxic hepatitis and progressive anemia developed but the patient eventually recovered In another case local bacteroides infection in a gangrenous leg probably led to thrombophlebitis with subsequent passage of infected emboli to the lungs and empyema formation In a case of post anginal septicemia with hectic fever pleurisy purulent arthritis hepatitis and massive subcutaneous abscesses internal jugular vein thrombosis occurred One patient with achalasia of the esophagus had a lung infection as a result of aspiration of material from the dilated esophagus Another patient had chronic pulmonary infection and probably cor pulmonale It seemed possible that perforation of the gastrointestinal tract led to abdominal abscesses with chronically draining sinuses due perhaps (not proved) to bacteroides in

(9) Am J M S 2 5 53273 M h 1953

plications but also in definite toxicity in acutely ill patients This toxemia is more distinctive than in infection caused by the other two species Infection with Br suis is much more likely to cause destructive and suppurating lesions resulting in a chronic form of illness whereas infection with Br abortus may cause toxicity or serious complications but the over all clinical picture is milder than in the other two forms of brucellosis

The failure of the antibiotics to eradicate brucella from the tissues of infected animals and the relapse of human patients after treatment suggest that the intracellular location of the organisms protect the bacteria against the action of the drugs Utilizing an in vitro technic Magoffin and Spink demonstrated that when suspensions of intra and extracellular brucella were exposed to streptomycin alone and in combination with aureomycin terramycin or chloramphenicol the leukocytes protected the organisms against the rapid lethal effect of these agents

Five patients with chronic brucellosis have been treated with ACTH Results have not been outstanding one way or another Two patients with acute brucellosis with bacteremia due to Br abortus have been treated with ACTH The first patients had been ill with fever for a month and coincident with ACTH administration the fever subsided bacteremia was no longer manifested and the patient recovered and has remained well for several months without a relapse The second patient had a much more dramatic response He had been ill for two months with a high fever and an enlarged and tender liver Within 24 hours of the first dose of ACTH he became alert and afebrile with few residua of toxicity The pain in the liver subsided and the organ became smaller ACTH was administered for several days during which time the patient felt well despite persistence of bacteremia When ACTH therapy was discontinued he became febrile Because of the bacteremia he was treated with dihydrostreptomycin and aureomycin He promptly recovered and has remained well for several months

It is concluded that in the critically ill and toxic patient with acute brucellosis ACTH may be used for 24 48 hours simultaneously with dihydrostreptomycin and aureomycin or terramycin

was a vague sense of resistance in the left upper abdomen Urine was sterile and a left retrograde pyelogram was normal She was treated for polycythemia vera which was also present During investigation of the left upper abdomen pain a perirenal insufflation was attempted When the needle was inserted into the perinephric space thick creamy pus was aspirated A mucoid Bacillus coli was cultured from the pus At operation a cortical renal and perinephric abscess on the left side was discovered and drained Recovery was uneventful

Chronic perinephritic abscess may be difficult to diagnose because of obscurity of symptoms and frequent lack of findings in urinary sediment especially with abscesses caused by staphylococci There are differences in bacteriology etiology and symptomatology in abscesses caused by staphylococci and those due to other pyogenic organisms Most common cause of perinephritic abscess is hematogenous localization of staphylococci in the renal cortex with resultant cortical abscess and subsequent involvement of the perinephric space Several weeks or days after an almost forgotten superficial infection the patient may become acutely ill with chill fever and lumbar pain or tenderness Urine may be free of organisms pus or blood

Perirenal abscess due to colon bacilli is rare When it occurs the chronic perinephritic lesion is generally obscured by active pyelonephritis or pyonephrosis due to obstruction calculi or other foreign body Since the introduction of antibiotics ravages formerly seen in acute pyelonephritis due to colon bacilli have largely disappeared especially in cases not complicated by obstruction or foreign bodies Although generally administration of antibiotics may lead to disappearance of both the pyuria and the bacilluria on rare occasions the drugs are ineffective In the reported case they failed to eliminate one focus of infection in the kidney which led to development of the abscesses

Pseudomonas Infections in Infants and Children Leo J Geppert Hinton J Baker Bernard I Copple and Edwin J Pulaski (Brooke Army Hosp Fort Sam Houston Tex) report eight ca es which illustrate that infections from Pseudomonas aeruginosa have become more common after the widespread and indiscriminate use of antibiotics usually penicillin Ecthyma gangraenosum hematogenous skin infections and noma are caused by this organism Of all the potentially pathogenic bacteria it is one of the most resistant to chemo

(2) J P d t 41 555 5(1 N mbe 195

fection A left pleural effusion in this case was at first sterile but later was replaced by bacteroides empyema Still another patient had otitis media mastoiditis lateral sinus thrombosis and probably metastatic lung abscesses and empyema due to Bacteroides funduliformis The patient recovered after treatment with aureomycin surgical drainage of a neck abscess and radical mastoidectomy One patient had a frontal lobe brain abscess and although the source of infection could not be determined with certainty neurosurgical drainage and penicillin and aureomycin therapy were successful A persistent leukocytosis was observed in many cases In one case ascending cholangitis was due to bacteroides infection and in another bacteroides empyema was believed to follow postoperative myocardial infarction mural thrombus pulmonary embolism and hemothorax from infarction in this order

In the diagnosis of bacteroides infections it is important to make a smear and Gram stain of the pus to detect the small gram negative bacilli which often do not grow out in mediums for several days even anaerobically and are apt to be overlooked

Successful therapy depends on a combination of carefully planned surgical and medical measures The surgical technic should include adequate drainage of all walled off foci and excision of all accessible necrotic tissue Sensitivity tests reveal a wide variation of the strains in their susceptibility to antibiotics In vitro and clinical studies indicate that aureomycin and terramycin are the most effective agents Prognosis of the infections has been improved since the advent of antibiotics

Perinephric and Renal Cortical Abscess Due to Colon Bacillus without Bacteriuria or Pyuria Kermit E Osserman and H Evans Leiter[1] report a case of chronic perinephritis and cortical renal abscess due to the colon bacillus without any apparent evidence of abnormality in the renal pelvis or urinary sediment

Woman 67 complained of fever pyuria and left upper abdominal pain Urine showed many white cells Intravenous and retrograde pyelograms revealed normal upper urinary tract She was treated with penicillin gantrisin® and aureomycin until fever and pyuria had disappeared Urine became sterile Two months later she complained of low grade fever and pain in the left upper abdomen There

(1) J Mt S a Hosp 19 4 4 427 July Aug 1952

lesion reveals rod shaped bacteria in the walls of the blood vessels at the site of infection This picture is similar to that described by Fraenkel in a study of 26 cases of pseudomonas infections of which 16 showed ecthyma gangraenosum

Treatment depends on in vitro sensitivity Despite its toxicity aerosporin[8] is indicated in severe infections in view of the poor prognosis provided the organism is sensitive to this antibiotic Combined therapy with penicillin strepto mycin and sulfadiazine may be effective even though the or ganism is moderately resistant to all three

In the eight cases of pseudomonas infection (noma pyo derma gangraenosum septicemia diarrhea acute upper and lower respiratory tract infections and chronic lower respira tory tract infection) the conditions developed after treatment with an antibiotic

CASE 1 —Boy aged 10 months hospitalized because of severe measles had been given penicillin for five days before admission The measles subsided after the usual course but because of secondary pneumonia he was given 100 000 units of penicillin twice daily On the 10th hospital day a bilateral ulcerating purulent conjunc tivitis developed with extreme swelling of both lid and sloughing of the lid margins Noma developed in the mouth and nose with sloughing of the palate and nasal septum The infant died and autopsy revealed multiple small submucosal abscesses throughout the colon and on the surface of both lungs Sections of these lesions were infiltrated with gram negative organisms identified on culture as Ps aeruginosa

CASE 2 —Boy aged 4 months was given penicillin and chloram phenicol for diarrhea Severe pyoderma gangraenosum developed followed by death

CASE 3 —Girl premature and weighing 4 lb was given 100 000 units of penicillin twice daily Numerous maculopapular nodules which became hemorrhagic and necrotic forming ulcers with rolled edges appeared over the entire body After P aeruginosa was recovered from the blood combined therapy with penicillin strepto mycin and sulfadiazine was given and the child finally recovered

CASE 4 —Girl aged 1 year was hospitalized because of diarrhea She had been treated previou ly for two weeks with 100 000 units of penicillin three times a day Stool cultures showed P aeruginosa The child died on the fourth hospital day Autopsy revealed ulcers of the small and large bowel and gram negative rods in the tissues which on culture were found to be Ps aeruginosa

Toxoid Immunization of Experimental Gas Gangrene W A Altemeier Robert Coith Roger Sherman M A Logan and A Tytell[3] (Univ of Cincinnati) report progress of in vestigations in development and evaluation of effective tox

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therapeutic and antibiotic agents Recognition of Ps aeruginosa lesions clinically is necessary to prevent a fatal outcome Cutaneous lesions are sufficiently characteristic to be recognizable on sight The primary lesion appears innocuous



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and resembles a small ecchymotic area which rapidly becomes necrotic and ulcerated The ulcer then spreads around the periphery with a minimal amount of reaction in the adjacent tissues (Fig 1) Although the patient may be afebrile blood cultures at this point are usually positive Pyemia and multiple metastatic lesions may develop (Fig 2) Biopsy of a

lesion reveals rod shaped bacteria in the walls of the blood vessels at the site of infection This picture is similar to that described by Fraenkel in a study of 26 cases of pseudomonas infections of which 16 showed ecthyma gangraenosum

Treatment depends on in vitro sensitivity Despite its toxicity aerosporin* is indicated in severe infections in view of the poor prognosis provided the organism is sensitive to this antibiotic Combined therapy with penicillin strepto mycin and sulfadiazine may be effective even though the or ganism is moderately resistant to all three

In the eight cases of pseudomonas infection (noma pyo derma gangraenosum septicemia diarrhea acute upper and lower respiratory tract infections and chronic lower respira tory tract infection) the conditions developed after treatment with an antibiotic

CASE 1 —Boy aged 10 months hospitalized because of severe measles had been given penicillin for five days before admission The measles subsided after the usual course but because of secondary pneumonia he was given 100 000 units of penicillin twice daily On the 10th hospital day a bilateral ulcerating purulent conjunc tivitis developed with extreme swelling of both lids and sloughing of the lid margins Noma developed in the mouth and nose with sloughing of the palate and nasal septum The infant died and autopsy revealed multiple small submuco al abscesses throughout the colon and on the surfaces of both lungs Sections of these lesions were infiltrated with gram negative organisms identified on culture as P aeruginosa

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oids for immunization against various types of gas gangrene Nature of injuries following atomic explosion or other catastrophe would lead to increased incidence of clostridial infections particularly gas gangrene clostridial myositis and tetanus Toxoids have been prepared for each of the principal bacteria capable of causing gas gangrene i e, Clostridium welchii Cl novyi Cl histolyticum and Cl septicum

The toxoid for Cl welchii has proved remarkably effective in experimental animals Guinea pigs are immune to severe challenge after three injections Inoculations in human beings have produced high antitoxin titers in the blood similar to those found in immunized animals A toxoid for Cl novyi has produced a high degree of immunity to experimental infections in animals Considerable progress has been made toward development of a suitable toxoid for Cl histolyticum but further studies are necessary before a satisfactory and effective preparation is possible

Under stress and with inadequate facilities for treating 40 000 80 000 casualties after an atomic catastrophe surgical treatment and antibiotic therapy conceivably might collapse to a large extent from sheer weight of numbers Surgery might often be delayed for 48 72 hours while treatment might be reduced to self help and mutual aid Unfortunately the first 72 hours after injury are most important and most cases of gas gangrene develop within this period Basic immunization of military and civilian populations with gas gangrene toxoid as well as tetanus toxoid should be carefully considered as a means of preventing tetanus and gas gangrene in mass casualties under conditions in which prompt and adequate surgical and antibiotic treatment would be lacking

Otitis Externa Bacteriologic and Mycologic Studies David E Singer Elizabeth Freeman Warren R Hoffert Reginald J Keys Roland B Mitchell and Albert V Hardy[4] examined 1 377 cultures taken from normal external ears and 646 taken from diseased external ears of military personnel at Tampa and Jacksonville Fla The 646 cultures were from 405 young men with otitis externa The *in vitro sensitivity* to seven therapeutic agents was determined on 3 071 bacteria isolated *Pseudomonas* other gram negative bacilli and streptococci were found rarely in normal but frequently in infected

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ears There was no increase in prevalence of other bacteria in the infected ear The pseudomonas group of organisms ap peared to be the most important etiologic agent Pseudomonas appeared in only 1% of normal ears and 65 5% of infected ears Members of the proteus group were isolated from 0 4% of normal ears and 7 9% of infected ears

Up to the past decade otitis externa was called otomycosis The earlier literature on this condition reported that mycotic infection was the cause In the present study mycologic find ings were predominantly negative If any fungi had even a minor etiologic role they would be the candida species not albicans and the aspergillus species

There is unanimity in the literature that otitis externa has a characteristic seasonal and geographic distribution It oc curs in the summer and is particularly prevalent in hot humid climates Swimming and trauma are predisposing factors

In vitro sensitivity tests pointed to terramycin and sulfa diazine as the drugs of choice

[This troublesome condition can be a great nui ance especially in children during swimming season Ointments containing polymyxin (aero sporin®) may be very effective again t the pseudomonas organisms —Ed]

Microbiologic Flora of Chronic Cutaneous Ulcers In Vitro Sensitivity of Microbiologic Flora to Three Antibiotics—Peni cillin, Streptomycin and Bacitracin Edward E Vicher John W Soska and George Gee Jackson[5] (Univ of Illinois) re port that the microbiologic flora of chronic cutaneous ulcers varies depending on the initiating cause of the ulcer its loca tion and its treatment Bacterial infection alone is rarely re sponsible for the ulcers but once the skin is broken by trauma or necrosis bacteria enter the fertile environment Infection adds to the severity of ulcers by exaggerating the necrosis extending the lesion and complicating closure Cultures were obtained from 63 decubitus ulcers in young persons hospital ized for paraplegia Among organisms isolated were hemo lytic Staphylococcus aureus 162 times micrococcus 144 times proteus 86 times pseudomonas 81 times diph theroids 73 times group D streptococcus 59 times Esch erichia coli and paracolon bacilli 33 times Aerobacter aerogenes 25 times alpha streptococcus 7 times achromo bacter 4 times and Klebsiella pneumoniae once The occur rence of gram positive organisms alone was common but of gram negative strains rare

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The in vitro sensitivity of 1,217 bacterial strains recovered from the ulcers was tested for penicillin, streptomycin and bacitracin Either bacitracin or streptomycin—about equally effective—far excelled penicillin in inhibiting staphylococci All antibiotics were effective against group D streptococci Penicillin and bacitracin were more effective than streptomycin against the diphtheroids Bacitracin was more effective than the other antibiotics against gram positive organisms Although streptomycin was more effective than penicillin against staphylococci and about equally effective against the other gram positive species resistant strains developed rapidly A large number of the proteus strains was sensitive to penicillin

Antibiotic therapy must be used on a clinical and individual basis with the understanding that open ulcers cannot be kept free from virulent or potentially virulent bacteria for long even with effective antibiotics Treatment should be intensive for short intervals dictated by bacteriologic cultures and centered primarily around surgical intervention or the need to control extension of the lesion by infection Antibiotics should not be used for prolonged prophylaxis since the result is a resistant bacterial flora

[The conclusions stated in the last paragraph are worth noting —Ed]

FORT BRAGG FEVER

Leptospiral Etiology of Fort Bragg Fever William S Gochenour Jr Joseph E Smadel Elizabeth B Jackson LaRue B Evans and Robert H Yager[6] (Walter Reed Gen l Hosp) summarize the status of Fort Bragg or pretibial fever a nonfatal febrile illness lasting approximately five days first described in summer 1942 among troops in North Carolina Headache malaise splenomegaly and fourth day erythematous rash limited to the pretibial areas characterize the illness About 40 cases were seen each summer for three years In 1944 Tatlock recovered an infectious agent from the blood of one acutely ill patient Although it grew well in embryonated eggs and specific antibodies against the agent appeared in the patient s convalescent serum various studies failed to show that the agent was related to a number of the more common viral and rickettsial agents The injection of

(6) Pub Health Rep 67 811 813 Aug t 195

this material into volunteers (after 80 passages in guinea pigs and 23 passages in egg) produced the typical illness after an incubation period of about one week

Recently a large collection of leptospiral strains assembled at the Army Medical Center made it possible to re examine immune serum from previous epidemics A high level of ag glutinating antibody against Leptospira autumnalis was dem onstrated Study of the actual infectious agent (by this time in its 365th passage) left no doubt that this was the organism Blood serum from 45 patients in the 1943 epidemic and 21 in the 1944 epidemic was tested and clearcut serologic evidence of infection with the leptospira was presented in 32 cases Members of this group of leptospirae were not previously known to occur in the United States

[It is remarkable that the causative agent was maintained in laboratories for years under the assumption that it was an ultramicroscopic virus until Gochenour and his associates demonstrated it to be due to a leptospira The same confusion occurred previously in the case of swineherd s disease first thought to be a viral meningitis later shown to be a lepto spiral meningitis —Ed]

TUBERCULOUS MENINGITIS

Incidence and Nature of Intracranial Calcifications after Tuberculous Meningitis John Lorber[7] (Univ of Sheffield) considers the rareness of intracranial calcifications after tuber culosis surprising considering the high incidence of intra cranial tuberculomas and of calcifying tuberculous lesions elsewhere in the body Skull x rays were taken on hospital ization of each child who had tuberculous meningitis and at three to six month intervals in all survivors for 2½ 4½ years after the onset of tuberculous meningitis No intracranial cal cifications were found on hospitalization or during treatment Intracranial calcifications were not demonstrated radiolog ically in 17 of the 25 survivors until 18 months or more from the start of treatment In 13 of the 17 the calcifications were not discovered until two to three years after the onset of meningitis

The lesions are divided into three different types accord ing to the situation and appearance of the calcified shadows The falx cerebri was calcified in two children but this is com

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mon under physiologic conditions in adults over 30 and it need not have been pathologic in the children In eight children the calcified lesions were apparently situated within the brain substance In 11 children more spectacular and less expected calcified shadows were found at the base of the brain Three children had more than one type of calcification

On the basis of the stage of meningitis on hospitalization no basal calcifications were seen in any of the 10 early cases but they were detected in 11 of the 15 children in the intermediate and advanced stages These observations correspond with Lorber s encephalographic studies which showed that obstruction of the cerebrospinal fluid pathways and tentorial blocks is rare in early cases whereas they may be found in over half the intermediate and in almost all advanced cases There was only slight correlation between intracranial calcifications and neurologic sequelae

Assuming that the calcifications are a sequel to tuberculous meningitis there are four possible causes They may represent calcified intracranial tuberculomas calcification in areas of healed tuberculous encephalitis or in areas of encephalomalacia after cerebral infarction or in tuberculous exudate in the meninges The eight intracerebral lesions described in survivors are probably calcified intracranial tuberculomas Their size and location correspond well with the description of the Rich foci and are quite unlike the more diffuse calcifications which occur after encephalitis or encephalomalacia The equal incidence of these intracerebral lesions in patients in different stages of meningitis on hospitalization favors the theory that these were the original Rich foci responsible for the meningeal dissemination The collection of calcifications in the basal cisterns indicates that they were calcifying organizing exudate of the meninges

It is estimated that in England alone about 300 400 patients are now cured annually of tuberculous meningitis Should intracranial calcifications eventually appear in about two thirds of them then tuberculosis may soon become one of the commonest causes of intracranial calcifications

[Antibiotic therapy in saving the lives of patients with hitherto fatal diseases has introduced some new clinical entities intracranial calcification due to healed tuberculous meningitis and a third kind of aortic insufficiency—healed acute bacterial endocarditis —Ed]

PROTOZOAN DISEASES

Cure of Korean Vivax Malaria with Pamaquine and Primaquine Paul L Garrison Daniel D Hankey Walter G Coker William N Donovan Bruno Jastremski (M C U S A) G Robert Coatney (U S P H S) Alf S Alving (Univ of Chicago) and Ralph Jones Jr [8] (Univ of Pennsylvania) present a study of 864 patients admitted to station hospitals with vivax malaria between July 1951 and May 1952 The diagnosis was established in every case by demonstrating parasites in the peripheral blood in two nonconsecutive smears

Three regimens were used in rotation Regimen A chloroquine—a total of 1 5 Gm chloroquine base was given in three doses of 0 3 Gm each during the first 24 hours followed by a single dose of 0 3 Gm daily for two days Regimen B chloroquine plus pamaquine—a total dose of 1 5 Gm chloroquine base was administered as in regimen A in addition 27 mg pamaquine base was given daily in three equally divided doses for 14 consecutive days Regimen C chloroquine plus primaquine—a total of 1 5 Gm chloroquine base was administered as in regimen A in addition 15 mg primaquine base was given in a single dose daily for 14 consecutive days

All patients were hospitalized for treatment and study and then followed as outpatients at intervals of approximately 6 weeks 709 were followed 4 11 months Sixty four of 232 patients on regimen A relapsed (27 6%) Only one of 246 patients on regimen B relapsed (0 4%) and none of 231 on regimen C The only toxicity noted was mild generalized pruritus in two cases and occasional mild crampy abdominal pain not sufficient to warrant stopping the drug

Primaquine is undoubtedly the drug of choice for curative treatment of Plasmodium vivax malaria because of the greater spread between the effective and toxic dose However either pamaquine or primaquine will cure most vivax infections without toxicity Since they are ineffective in destroying the erythrocytic stage of the parasite these drugs should be given simultaneously with chloroquine for treatment of the acute attack Because of the greater toxicity of pamaquine in Ne

(8) J A M A 149 156 1563 A g 23 195

mon under physiologic conditions in adults over 30 and it need not have been pathologic in the children In eight children the calcified lesions were apparently situated within the brain substance In 11 children more spectacular and less expected calcified shadows were found at the base of the brain Three children had more than one type of calcification

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the central nervous system and major thoracic and abdominal viscera involved Muscle biopsy is an excellent diagnostic aid

The clinical syndrome in adult toxoplasmosis consists of fever maculopapular rash—sparing scalp palms and soles—and headache There may be cough arthralgia and myalgia lymphadenopathy pneumonitis and conjunctivitis but no central cerebral calcifications or chorioretinitis There is leukopenia or a normal leukocyte count The distribution of the myositis the myocarditis the lesions in the central nervous system and the petechial skin eruptions are all indicative of a hematogenous spread of the infecting agent Antibodies may not appear until late in the course of the disease A few persons with toxoplasmosis have recovered and in some of them infection has been extremely mild The relatively high incidence of antibodies suggests that toxoplasmosis is a common disease which usually assumes the form of a mild infection with few symptoms Rarely will such a florid example of the disease as the one here reported be encountered in an adult

[An excellent study of a case This kind of infection may eventually prove to be of greater importance than we can demonstrate today Danish workers have suggested that milder forms of toxoplasma infection can resemble infectious mononucleosis —Ed]

Parenchymal Amebiasis Clinical Study is presented by Martin J Freedman and Edward A Cleve[1] (Letterman Army Hosp San Francisco) Reports indicate that the incidence of infection with Endameba histolytica is high in every climate that extraintestinal spread will develop in nearly 20% of cases and that liver involvement is present in up to 56% of clinical cases of amebic dysentery The early liver abscess may be small and solid but later it becomes gelatinous and eventually filled with characteristic chocolate colored or anchovy pastelike material Symptoms arising from amebic infection of the liver vary according to the stage of the disease and the rapidity of its spread Hepatitis may be present in the acute subacute or chronic form frank abscess may be acute or chronic Large amebic abscesses of the liver often produce palpable masses in the epigastrium They may grow so large as to be visible on gross inspection Some may rupture either externally or into surrounding tissues Most abscesses rupture into the pleural cavity and lung although they may perforate into the peritoneum mediastinum pericardium stomach colon

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groes this drug should not be used unless the hemoglobin level is observed closely

[This seems to be the best therapy devised for malaria to date—Ed]

Toxoplasmosis in the Human Adult According to Edward H Kass Stephen B Andrus Raymond D Adams and Frank C Turner (Boston) and Harry A Feldman[9] (Syracuse N Y) most cases of toxoplasmosis reported have been in infants A few cases in adults have been described but the clinical picture has differed from the infantile form in that a maculo papular rash and evidence of pneumonitis acute encephalitis and myocarditis were prominent whereas cerebral calcifica tions and chorioretinitis were absent A case of toxoplasmosis in a human adult is described (1) diagnosis was suggested by the histologic examination of a muscle biopsy specimen (2) toxoplasma organisms were isolated from the specimen (3) diagnosis was reached in time to institute intensive therapy with several agents that had proved effective in animals (4) serial antibody determinations indicated that this was a re cently acquired infection (5) a complete postmortem exam ination demonstrated disseminated polyomyositis and me ningoencephalomyelitis and (6) the organisms were isolated from many organs

Woman 60 had experienced malaise and fatigue 10 12 days before hospitalization then dull aching pains in both knees hips and in the vertebrae a few days later and finally a macular rash had appeared all over the body and had been present for 4 5 days Tem perature was 104 6 F she had a fading brown macular ra h over the trunk and extremities and the white cell count was 7 440 She was in the hospital for 60 days Temperature fluctuated between 99 and 104 F with daily spiking elevations Despite treatment with full courses of aureomycin penicillin streptomycin sulfadiazine corticotrophin and chloroquine she died A muscle biopsy specimen before death revealed histologic features of toxoplasmosis and the organism was isolated from the muscle by animal inoculation Dye test antibodies were absent in a serum obtained on the 2d hospital day but were present to a dilution of 1 16 384 on the 36th and 43d days and to 1 32,768 on the 61st day

Although medications failed to alter the outcome of the disease they may have helped for few fresh lesions were noted at autopsy Corticotrophin may have lowered the re sistance to infection thereby decreasing the effectiveness of some of the chemotherapeutic agents Autopsy revealed that lesions and organisms may be extremely widespread with

(9) A M A A h I t Med 89 59 78 M y 1952

patients with active amebic diarrhea or dysentery in New Orleans and Calcutta Endameba histolytica was demonstrated in every instance Terramycin was the only specific therapy given initially although two patients subsequently received other drugs Symptoms were promptly controlled in all instances Frequency of stools was greatly reduced often within 24 hours Except in one case stools from the fourth day on contained no parasites blood or mucus and sigmoidoscopy revealed healing of the ulcers Follow up studies for parasitologic cure were short and inadequate Toxicity to terramycin was encountered in five patients who had nausea vomiting or diarrhea

These results are less optimistic than those previously reported since one patient had parasites at the end of 1 month and another at 2½ months However these patients may have been reinfected The promptness of clinical response to terramycin indicates a definite place for this drug in the treatment of diarrheal and dysenteric amebiasis Emetine may be satisfactorily replaced by terramycin since it is less toxic and probably more effective Aureomycin may also be satisfactory

Trichomonas Vaginalis in the Male Experimental Infection of a Few Volunteers According to F Lanceley and M G McEntegart[3] (St Luke s Clinic Manchester) there is little general agreement on the subject of T vaginalis infection in the male urogenital tract The occurrence of the same parasite in the male as in the female is important whether or not it causes symptoms Examinations have shown that although most infected husbands were symptom free they were a potential source of reinfection of successfully treated wives The infection in males is almost always venereal Little is known about its incidence

A strain of T vaginalis was isolated from a patient with vaginitis and maintained in a bacteria free culture in a special medium Two cc of the medium was injected with a pipet into the urethra of five male volunteers The bacteriologic sterility of the culture was confirmed both aerobically and anaerobically In five male controls 2 cc of the sterile culture medium was injected into the urethra The controls were examined daily for three weeks and at no time was any urethral irritation or infection found nor was T vaginalis demonstrated in urethral scrapings urine or prostatic fluid

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or other neighboring structure About 13% rupture into the peritoneum

Amebic abscess of the brain is rare About 88 cases have been reported of which 27 have been confirmed histologically or bacteriologically Most cases have been associated with abscess of the lung or liver and in some cases metastasis to the brain occurs after surgery on liver abscesses

Excessive fibrosis in cases of chronically exacerbating amebiasis may cause cicatricial stenosis of the bowel simulating carcinoma clinically This may occur as a localized narrowing or involvement of a great length of the intestine and give rise to symptoms of total or partial obstruction When possible preoperative treatment with amebicides is advisable

Granulomatous lesions from amebiasis sometimes invade the skin producing extensive destruction and tissue slough This may occur after drainage of an abscess or may be secondary to a focal fistula or colostomy

Man 55 had had chronic diarrhea with intermixed blood and mucus for six months He complained of recurrent abdominal cramps and anorexia and had lost 30 lb Sigmoidoscopy revealed an annular constricting mass about 10 cm from the anal orifice which would admit only the tip of the index finger Biopsy revealed chronic inflammation Stool examinations were negative for amebas and sigmoid colostomy was performed The abdominal wall around the colostomy began to slough in 14 days Excision of the ulcerated area was followed by skin grafts which did not take The patient was given emetine 0 66 Gm daily for eight days followed by diodoquin* The wound rapidly became clean and healing began A month later another skin graft was placed with an excellent take The patient improved rapidly and within six months the rectal mass had disappeared

Amebiasis extending from the cecum to involve the appendix may often produce symptoms closely simulating those of acute appendicitis Surgery may lead to disastrous results In the Chicago epidemic of 1933 13 of 32 patients on whom appendectomy was done died

Because patients infected with E histolytica often undergo dramatic cures with proper therapy a high index of suspicion should be maintained whenever suggestive symptoms occur Therapeutic trial is often indicated in the absence of a proved diagnosis

Terramycin in Active Diarrheal and Dysenteric Amebiasis W A Sodeman (Tulane Univ) R N Chaudhuri and D Banerjee (Calcutta) report their experience in treating 16

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In three of the five men inoculated intraurethrally with a pure culture of T vaginalis urethritis developed and the protozoa were recovered for 4 44 and 94 days respectively Trichomonas vaginalis was first observed on the sixth and ninth days Two of these patients who had severe urethritis had prostatitis also The other two volunteers had mild transient urethritis but no trichomonads were recovered With one exception none of the volunteers complained of symptoms during the experiment

Examination of carefully taken urethral scrapings often revealed trichomonads when they could not be demonstrated by any other method This may be an important test for diagnosis and cure since the patient may transmit the disease as long as the protozoa persist Examination of the serum of the volunteers failed to demonstrate antibody to the protozoa

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MYCOTIC INFECTIONS

Treatment of Central Nervous System Cryptococcosis Review and Report of Four Cases Treated with Actidione® Charles A Carton[4] (Columbia Univ) points out that 70% of patients with this disease die within the first three months and 86% die within the first year However a small number of patients with apparently indolent central nervous system infections survive up to nine years with positive cerebrospinal fluid cultures

A vast number of therapeutic agents have been tried Since actidione® was discovered by Waksman and associates in 1945 while working with Streptomyces griseus its antifungous activity has been noted and 10 patients with cryptococcosis have been treated with intramuscular doses ranging from 10 mg twice a day to 30 mg four times a day Intrathecal injections up to 10 mg daily and intraventricular injections up to 30 mg daily have also been used Although the drug appeared to affect the temperature curve favorably in several patients all died except one Two observers noted sterilization of the cerebrospinal fluid Although the drug has a very high inhibitory titer in vitro against the cryptococcus in animals it provides no protection from experimental infection

(4) Ann I t M d 37 123 134 J ly 1952

Two of four patients showed definite improvement in clinical and laboratory status during actidione* therapy one apparently being cured The two others showed no response and both died of fulminating meningitis Toxic manifestations do not prevent use of the drug by intramuscular intravenous or intrathecal routes provided reasonable care is taken It is apparent that actidione* is not very effective against central nervous system cryptococcosis However until a better antifungous agent is available it should be tried with caution coupled with fever therapy if possible

Treatment of Systemic Blastomycosis with Stilbamidine Emanuel B Schoenbach (New York City) Joseph M Miller (Fort Howard Md) and Perrin H Long[5] (New York City) report results with stilbamidine and propamidine in four cases of blastomycosis with beneficial results in three The literature contains reports of 347 cases If patients who were followed for less than two years are excluded the mortality rate is 92% The cutaneous type proceeds by chronic ulcerations and usually responds to treatment with iodides or radiation The *systemic type is characterized by widespread pulmonary* and visceral lesions Iodides may be dangerous in this form unless hypersensitivity is excluded by the skin test Stilbamidine was tried because diamidines are known to exert a fungistatic effect on Blastomyces dermatitidis Stilbamidine a water soluble white crystalline powder unstable on exposure to light is administered by slow intravenous drip after fresh preparation Acute toxicity may result in circulatory depression salivation and incontinence Late chronic toxicity is confined to a unique neuropathy usually sensory loss confined to the tace

Man 26 was hospitalized after dysphagia for one year had caused 40 lb weight loss X rays revealed a stricture and biopsy of a malignant looking lesion on two occasions failed to show neoplastic cells Cultures revealed a yeast thought to be a contaminant and he was transferred to another hospital with the diagnosis of carcinoma There a third biopsy revealed blastomyces He was given a low protein low purine diet and 5 cc of 0 1% propamidine in 5% glucose was inserted into the fistula and 0 1 Gm stilbamidine in 100 cc of 5% glucose was given slowly intravenously Streptokinase and streptodornase were applied topically The temperature gradually declined and the inflammatory reaction receded considerably A course of 15 days of 0 15 Gm stilbamidine daily each month for 3

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(4) A I t M I 37 1 3154 J ly 1952

Of 24 patients who received supportive therapy alone 14 had neurologic sequelae of some sort these were more severe than those in patients who received antibiotic therapy Of 13 patients treated with antibiotics 6 had residual neurologic damage Only one of seven patients receiving antibiotics within the first three days of rash had an abnormal EEG

In some patients the acute changes are reversible with convalescence in others residual damage persists longer than a year and may be assumed to be permanent

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VIRAL RESPIRATORY DISEASES

Further Studies on Natural Transmission of Common Cold are reported by J E Lovelock J S Porterfield A T Roden T Sommerville and C H Andrewes[7] (Harvard Hosp Salisbury England) Although results of investigations have indicated that the common cold may be transmitted from man to man by instillation into the nose of bacteria free filtrates of infective nasal washings this information throws little light on the ways in which colds are transferred under natural conditions Experiments were therefore carried out to determine whether colds could be transmitted by droplet nuclei alone or by indirect contact alone these conditions being compared with full exposure all normal routes of transference being allowed to operate

Volunteers who had been examined for three days and found to be free from cold were selected as experimental subjects Persons with colds of recent onset were chosen as donors Two colds developed in 25 volunteers exposed to droplet infection three in 32 exposed to full contact with donors and two in 25 exposed to a contaminated environment

Infected material from persons with colds was transmitted by means of a mist to volunteers The results of the spraying tests indicated that the common cold virus can survive the spraying and that a cloud of infected droplets will produce colds in some of the persons exposed Infective secretions were placed around the outside of the nose of some of the subjects It appeared that this procedure is unlikely to produce a cold

An average of 50% of volunteers may be expected to have

(7) La t 2 657 660 Oct 4 195

months resulted in decided general improvement 37 lb weight gain and complete recession of the inflammatory condition Biopsy failed to show blastomyces Six months later the improvement was continuing but facial numbness had appeared The pulmonary infiltrations showed remarkable reduction although esophagrams revealed persistence of an esophageal stricture

Similar beneficial results were obtained in several other cases of blastomycosis The authors believe that further clinical usage of stilbamidine is warranted

[This seems much the most promising treatment yet found for blastomycosis —Ed]

RICKETTSIAL INFECTION

Residual Effects of Rickettsial Disease on Central Nervous System Results of Neurologic Examination and Electroencephalograms Following Rocky Mountain Spotted Fever are reported by Marvin J Rosenblum Richard L Masland and George T Harrell[6] (North Carolina Baptist Hosp Winston Salem) Rocky Mountain spotted fever one of the severest of all infectious diseases is a specific generalized intracellular infection of small peripheral blood vessels The extent of damage in the skin and subcutaneous tissues can be easily followed and the completeness of repair readily evaluated but it is difficult to estimate the extent of the acute lesions and degree of residual damage in the central nervous system Neither the clinical findings nor results of cerebrospinal fluid examination during the acute phase of the illness make it possible to predict which patients will have permanent damage After convalescence residual brain damage may be manifested clinically by loss of memory pronounced mental retardation behavior disorders or even convulsions

Thirty seven patients were examined one to eight years after the acute phase of the disease Some type of neurologic sequela was found in 21 Fourteen had a history of neurologic symptoms 6 had neurologic signs and 12 had abnormal EEG s Twelve additional patients had borderline EEG abnormalities A high proportion of patients who had had fever for more than 10 days had abnormal EEG s Of 15 patients who had abnormal neurologic signs during the acute illness 3 had residual signs and 2 had convulsions

(6) A M A Arch Int Med, 90 444-455 Oct 1952

Physical signs were more useful than symptoms in separating the groups Examination of the group with infiltration revealed pharyngitis (67%) fine rales (100%) coarse rales (58%) dulness (75%) diminished breath sounds (62%) friction rub (8%) dyspnea (4%) conjunctival injection (71%)—all much more frequent than in patients without in

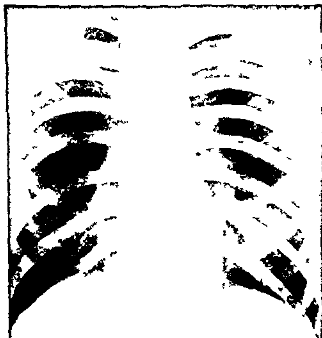


Fig 3—H l oot p m ent w th per h la b h va cula t ia io tend g t base w th f p hym l filt t t l ft fourth a t t p (Court y f S ber J M d J rus ew k E A M A Arch I t Med. 90 01 216 A g t 195)

filtration X rays at time of hospitalization showed the infiltration in 87% Influenza antibodies rose at least fourfold in paired serums in 67% of those with infiltration and in 87% of those without Cold agglutinins rose over a titer of 320 in three patients with infiltration and in one without X ray revealed bronchitic lesions denoted by increased density of one or both hilar shadows with prominent bronchovascular mark

colds after instillation of infected drops into the nose irrespective of age frequency of natural colds or time since last cold This suggests that experimental infection of volunteers with a given quantity of virus might be more readily achieved by exposure to infected droplets than by other methods

Although common cold infection may spread from person to person by normal social contact and through the air in the form of droplet nuclei the rate of clinical cross infection is low There is no evidence to suggest that spread by indirect contact is of major importance in the natural transmission of the common cold The number of volunteers infected as a result of direct contact compare favorably with the natural rate of cross infection that they are fewer is not surprising in view of the fact that there was only a single period of exposure in the experiment

It is probably true that development of an overt cold in man is determined more by the varying susceptibility of the person than by the degree of exposure to the causal agent

Virus Influenza A Infection with Pulmonary Manifestations Jordan M Scher and Edward Jaruszewski[8] (U S Nav Hosp Philadelphia) report the clinical manifestations of a *three month epidemic involving 76 cases* There are few reports of a pneumonic infiltration in uncomplicated virus influenza However 32% of the patients in this epidemic had infiltrations demonstrable roentgenographically and clinically

A diagnosis of influenza virus infection was accepted when there were (1) serologic evidence of a high or rising titer against influenza virus (2) a compatible clinical course and (3) absence of bacterial pathogens as etiologic agents Average age of the patients meeting these criteria was 26 5 Those with pulmonary infiltration averaged 22 3 years and were hospitalized 17 6 days compared with 13 2 days for those without infiltration All patients with infiltration experienced cough compared with 71% in the group without infiltration Pleural pain (37 5%) chills (75%) fever (100%) blood streaked sputum (29%) in patients with infiltration were all more frequent than in patients without infiltration Most other symptoms such as retro orbital ache muscular pain nausea vomiting rhinorrhea substernal pain and photophobia were slightly more frequent in the patients with infiltration

(8) A M A Arch Int Med 90 01 16 Aug 1 195

rash was seen None of 31 persons who had previously had measles during stays in Denmark contracted the disease again Only 5 unprotected persons of altogether 4 262 (4 320 less 31 having previously had the disease less 27 prophylactically treated persons) escaped the disease—a morbidity of 999/1 000

The type of complication did not differ from those usually associated with measles in Denmark Of 1 657 patients not treated prophylactically 45 7% had complications The most frequent type was of the lungs 35% of the males and 45% of the females showing symptoms of pulmonary involvement Ear complications were next in frequency accounting for one tenth of all complications Heart failure was the most serious complication and accounted for 2 2% of all complications Encephalitis was seen in six patients of whom four died

The specific death rate for the epidemic was 18/1 000 16/1 000 for males and 20/1 000 for females One third of the deaths were due to heart failure one fifth to tuberculosis and one sixth to pneumonia

Measles and tuberculosis —An examination for tuberculosis had been made in one of the largest villages shortly before the epidemic An examination after the epidemic in September showed 19 new cases of tuberculosis among 352 persons 13 of the patients had positive sputum Among 58 persons known to have tuberculosis before the epidemic 9 died and 13 showed progression of the lesions at the second examination These figures seem to justify the conclusion that measles causes reduced resistance to tuberculosis Tuberculin allergy appeared temporarily reduced or absent during measles infection

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POLIOMYELITIS

Comparison of Clinical Features of Poliomyelitis in Adults and in Children. Louis Weinstein Alexis Shelokov Raymond Seltser and Gordon D Winchell[1] (Boston Univ) compare adult and childhood poliomyelitis in 428 patients hospitalized from May through December 1949 Because of the increasing frequency among adults the term infantile paralysis is no longer applicable Patients were divided into four age groups 0 5 6-15 16-30 and 31 50

(1) N w E gl d J Med 246 296 301 F b 21 195

ings extending from the hili in 46% of those with infiltration Seven had peribronchitic lesions extending into the cardio phrenic angle five had alveolar infiltrations obscuring the linear markings and only one patient had a denser consolida tion suggestive of lobar consolidation Figure 3 illustrates a typical x ray picture of infiltration

In certain cases the fever and symptoms quickly subside despite persistence of the pulmonary infiltration for as long as 15 days Such a course should suggest virus influenza infec tion The diagnosis primary atypical pneumonia might bet ter be reserved for those more prolonged remittently febrile and debilitating cases

[Areas of pneumonitis were noted with greater frequency in the recent influenza A epidemics than in most previous outbreaks of influenza This strain of the virus may differ from others in that respect —Ed]

MEASLES

An Epidemic of Measles in Southern Greenland, 1951 Measles in Virgin Soil In discussing this measles epidemic Povl Elo Christensen Henning Schmidt Oskar Jensen H O Bang Vera Andersen and Bjarne Jordal[9] (Copenhagen) point out that according to available facts it is the first time such an epidemic has gained a foothold in Greenland On Apr 26 1951 a young Greenlander a sailor was found to have measles The area hit by the epidemic comprised the most southern part of the inhabited coastal area of West Greenland The population is of mixed Greenland European ancestry with very few pure Eskimos A total of 4 475 Greenlanders and 139 Danes live in the community

The epidemic proper —As soon as the Danish government realized that an epidemic of such a contagious disease as measles was imminent physicians and trained nurses as well as medical supplies were sent The sailor who first had measles left Copenhagen 19 days before the appearance of the skin rash and arrived in Greenland 10 days before measles was diagnosed He had come in contact with many people during his visit and at a dancing party Of 4 320 registered inhabi tants of the community 4 221 finally had typical measles 36 are thought to have been infected despite the fact that no

(9) Acta med sc d a 144 313 3 430 449 450 454 195

disclosed that children under age 5 had palsy of one leg three times as often as the adult group Quadriplegia was not ob served at all in the very young children and was 2½ times more common in adults than in older children The paralyses that endanger life are most common among young adults Death rate in adults is nine times higher than in children (Table 2) The incidence of pregnancy in the adult poliomy elitis group was at least four times higher than expected

TABLE 3—CLINICAL DIFFERENCES IN POLIOMYELITIS IN ADULTS AND CHILDREN 4 8 HOSPITALIZED PATIENTS 1949

Cli c F tu	Ch n	A u
S d n	M m l	M f m l
Sev ty	R l t ly m ld	S
C mm t p d m	Upp p fe t n	G pp
Ch ll	U mm	Comm n
G t t t l d t b n	U mm n	C mm n
Bl dd p ly	U mm n	C mmon
L mph d p thy	C mm n	U mm n
Sk e pt on	Un mm n	C mm n
C mm t typ f b lb d	N IX X VII	N VII IX X III IV VI d m d ll
C mm t p ly s f t m t	O e l g m	B th m d both l g b th m
P ly f p at y m l	Abo t 10%	About 40%
P ly f m l f b dom d b k	Abo t 20%	Ab ut 35%
Cy o	R r	C mm

assuming that 7% of women of the age group 16 30 years are pregnant at any given time A summary of the chief clin ical difference in poliomyelitis in adults and children is pre sented in Table 3

[This is a valuable collection of information and points up some strik ing differences in the manifestations of poliomyelitis in adults and children It is surprising to note the frequency with which rashes were found in adults —Ed]

Relationship of Surgery of Nose and Throat to Poliomy elitis was studied by Alden H Miller[2] (Univ of Southern California) who made a statistical survey of all cases of poliomyelitis in Los Angeles County during 1949 50 Tonsil lectomy and adenoidectomy were the only nose and throat operations noted with any degree of frequency Yet of 3 601 patients with poliomyelitis only 20 (0 5%) had had recent tonsillectomy and adenoidectomy There was no significant difference in the incidence of poliomyelitis among the patients who had had these operations and the expected incidence in a similar age group even during the summer months of high est poliomyelitis incidence

(2) J A M A 150 53 534 Oct 11 1952

Prodromal manifestations of sore throat fever and other complaints suggestive of an upper respiratory infection were commonest in the youngest age group and became less frequent with increasing age decreasing from 36% in the youngest to 9 6% in the oldest group Symptoms of mild gastrointestinal upset before appearance of signs of meningeal irritation on the other hand were twice as common in adults as in children The grippe prodrome generalized aching and fever without

TABLE 1—SYMPTOMS AND SIGNS OF POLIOMYELITIS IN VARIOUS AGE GROUPS

SYMPTOM OR SIGN	% OF PATIENTS BY AGE GROUP			
	0 5 Yr	6 15 Yr	16 30 Yr	31 50 Yr
Stiff neck	46%	84 4%	88 5%	90 4%
Headache	38	79 5	85 0	90 4
Muscle pain	32	41 0	58 1	55 8
Sore throat	32	26 7	33.3	13 5
Chills	4	12 4	29 7	26 9
Difficulty in swallowing	6	20 5	17 0	19 5
Difficulty in urination	2	5 6	26 1	25 0
Irritability	26	6 9	3 2	3 8
Chest pain	0	1 9	4 2	5 8
Bladder paralysis	4	3 1	3? 1	28 8
Lymphadenopathy	20	24 2	12 1	7 7
Gastrointestinal dysfunction	4	2 5	17 0	19 3
Cyanosis	2	2 5	10 9	13 5
Rash	2	1 9	7 3	38 5

TABLE 2—FATALITY RATES IN VARIOUS AGE GROUPS

AGE	NO OF PATIENTS	DEATHS	
		No	%
0 5	50	0	0
6 15	161	2	1.3
16 30	165	14	8 6
31 50	5?	4	7 7

localizing signs occurred in 33% of the oldest group and 22% of the youngest There was complete absence of prodrome in 42% of the oldest group and in only 32% of the youngest Many symptoms showed no significant differences in incidence among the various groups These included fever back stiffness vomiting weakness constipation malaise hyperesthesia dizziness diplopia and drowsiness

Table 1 lists the physical findings in different age groups Lymphadenopathy was more common in childhood Meteorism bladder paralysis cyanosis and rashes were much more common in adults Comparison of the degree of muscle paralysis

The number of poliomyelitis cases was too small to determine whether gamma globulin had afforded any protection

2 Conduct and early follow up of 1952 Texas and Iowa Nebraska studies—Hammon Cornell and Stokes[4] report that from experience gained in the 1951 pilot tests minor modifications were made for the definitive 1952 tests but that in all essentials the tests were similar so that results of all could be combined for analysis In July 1952 33 137 children aged 1 6 in Harris County Tex and 15 686 children aged 2 11 in Woodbury County Ia and Dakota County Neb received injections of either Red Cross gamma globulin or gelatin Co-operation and participation by the medical profession and the public were most encouraging The epidemics selected have continued in such a manner that 85 cases have occurred already in the inoculated group and cases continue to occur The number should be large enough for highly significant conclusions to be made

3 Preliminary report of results based on clinical diagnosis—Hammon Cornell Paul F Wehrle Christian R Klimt and Stokes[5] present a preliminary evaluation of results in 54 772 children aged 1 11 half of whom received gamma globulin and half gelatin As of Oct 1 1952 90 cases of paralytic poliomyelitis had been diagnosed Only 26 occurred in children given gamma globulin During the first week after injection gamma globulin did not appear to offer any significant degree of protection as 12 cases occurred in the group given gamma globulin as compared with 16 in those given gelatin However the severity of the paralysis appears to have been modified From the second through the fifth weeks highly significant protection was demonstrated After the fifth week this was less evident but more definite conclusions regarding the duration of protection and possible modification of disease should be available after a longer follow up Further laboratory studies will give information regarding the effect of gamma globulin on inapparent infection and the subsequent development of active immunity

Studies in Human Subjects on Active Immunization against Poliomyelitis Jonas E Salk[6] (Univ of Pittsburgh) reports preliminary results of studies on human subjects inoculated

(4) J A M A 150 750 756 Oct 25 1952
(5) Ibid pp 757 760
(6) Ibid 151 1081 1098 M 8 1953

A separate survey revealed that only 30% of 675 polio myelitis patients studied had had tonsillectomy and adenoidectomy at any time Since one of every three of the general young population has had these operations this figure is no more or less than could be expected

The bulbar type of poliomyelitis consistently developed at least twice as often in patients operated on less than 30 days before onset of the disease than it did in the remainder of the poliomyelitis patients Tracheotomy and a respirator were required twice as often in these patients as in persons who had not undergone tonsillectomy

Evaluation of Red Cross Gamma Globulin as Prophylactic Agent for Poliomyelitis—*1 Plan of controlled field tests and results of 1951 pilot study in Utah*—William McD Hammon (Univ of Pittsburgh) Lewis L Coriell and Joseph Stokes Jr[3] (Univ of Pennsylvania) review results of animal experiments which indicated that passive prophylaxis of human poliomyelitis is theoretically feasible Human gamma globulin prepared from large donor pools of plasma collected from extended geographic areas has been shown to have an equal titer of antibody for all three known types of poliomyelitis virus Field tests were conducted to determine whether gamma globulin given in reasonable dosage before onset of the naturally acquired disease would prevent paralysis The plan of study involved giving half of a group of children injections of gamma globulin and the other half injections of a gelatin solution No one would know at the time which children had received gamma globulin The test would be made on a volunteer group in an epidemic area About 50 000 children would have to be included in the study to insure statistically significant results

A pilot study was conducted in Utah County Utah in September 1951 during which 5 767 children received injections The study was approved by the medical and public health professions at the state and local levels The public response was phenomenal as regards co operation and participation There were no serious difficulties in carrying out the study and no significant clinical reactions There was no evidence that the inoculations led to any increase or localization of paralysis

(3) J A M A 150 739 749 Oct 25 195

possible to infect hamsters consistently by the intraperitoneal route after cortisone treatment A rapidly progressing highly fatal disease developed the severity of which equaled and possibly exceeded that obtained on intracerebral inoculation of the virus into cortisone treated hamsters Disease could not be produced in hamsters receiving no cortisone There was a clearcut reciprocal relation between amount of cortisone used and concentration of virus necessary for production of the disease By proper adjustment of these two variables an incubation period as short as three days and a mortality of 100% could be obtained In contrast to cortisone ACTH in large doses failed to modify the poliomyelitis resulting from intracerebral injection of the virus and disease could not be produced by the intraperitoneal route Of special interest is the fact that the cortisone treated hamsters have extraneural multiplication of the virus with a viremia which is not observed when the virus is injected intracerebrally Induction of the infection by the intraperitoneal route offers a new method for testing the neutralizing potency of serums and for investigation of chemotherapeutic agents By adjusting the dose of cortisone one can produce epidemics of predictable severity

[This is about the only instance so far observed of enhancement of a viral infection by cortisone —Ed]

VARICELLA

Varicella Pneumonia Samuel Saslaw John A Prior and Bruce K. Wiseman[8] (Ohio State Univ) observed a severe virus type of pneumonia with extensive bilateral nodular pulmonary infiltrates in three adults with chickenpox The patients aged 28 38 and 12 had similar nodular pulmonary infiltrates which were in all probability caused by the varicella virus The paucity of pulmonary findings on physical examination was in distinct contrast to the extensive infiltration seen roentgenographically (Fig 4) The clearing of the lung fields paralleled improvement in the skin lesions although one patient had some residual infiltration two months after onset of the varicella pneumonia All patients had negative blood cultures Results of sputum examinations were not consistent with those observed in bacterial pneumonia Leukocyte counts

(8) A M A A h I t M d 91 35 4 J y 1953

with different experimental poliomyelitis vaccines For preparation of these vaccines virus of each of the three immunologic types was produced in cultures of monkey testicular tissue or monkey kidney tissue Before the subjects were inoculated the virus was made noninfectious for the monkey by treatment with formaldehyde From one series of experiments it appeared that antibody for all three immunologic types was induced by inoculation of small quantities of the vaccines incorporated in a water in oil emulsion In another series antibody formation was induced by intradermal inoculation of aqueous vaccines containing the type 2 virus The antibody so induced persisted without signs of decline for the longest interval studied so far i e 4½ months after the start of the experiment

Data obtained from a comparison of levels of antibody induced by vaccination with levels that developed after natural infection indicate that it is possible with a noninfectious preparation to approximate the immunologic effect induced by the disease process itself

Although the results of these studies can be regarded as encouraging they should not be interpreted to indicate that a practical vaccine is at hand It will be necessary to establish precisely the limits within which the effects described can be reproduced with certainty

Because of the great importance of safety factors in studies of this kind considerable time is required for the preparation and study of each new batch of experimental vaccine before human inoculations can be considered This fact above all else imposes a limitation in the speed with which this work can be expanded Within these limits every effort is being made to obtain the necessary information that will permit logical progression of these studies into larger numbers of persons in specially selected groups

[It is obvious now that vaccines can be prepared which will be safe and which will induce formation of antibodies against the different strains of virus We wonder of course how long the induced immunity will persist since repeated vaccination of the general population would never be practicable —Ed]

Poliomyelitis Infection in Cortisone-Treated Hamsters Induced by the Intraperitoneal Route Gregory Shwartzman[7] (Mount Sinai Hosp New York City) demonstrates that it is

(7) Proc Soc Exper Biol & Med 79 573 576 Ap 1 1952

four years ago Similar in size and biologic properties to poliomyelitis virus they are extremely prevalent in children in the summertime Unlike many human viruses they can be demonstrated with ease in a cheap and widely available laboratory animal—the suckling mouse An extensive literature related to their properties and occurrence in man has appeared during the past four years

Viruses can be classified according to type of disease they produce in the sucklin mouse Group A viruses which include 8 11 serologically distinct types characteristically produce extensive liquefaction necrosis of skeletal muscles and virtually no other pathologic changes Group B viruses were originally so classified when Dalldorf found that they produce only mild to moderate focal muscle lesions while causing characteristic encephalopathy and panniculitis Pappenheimer has shown that some strains of group B produce exten ive pancreatitis as well as other visceral lesions

All the Coxsackie viruses appear to be extremely small on the order of viruses of poliomyelitis and murine encephalomyelitis All strains exhibit complete resistance to ether penicillin streptomycin and chloramphenicol

Diagnosis of Coxsackie virus infections remains the prerogative of research laboratories equipped to attempt large scale isolations and typing of viruses

Most early reports concerned with Coxsackie viruses stressed occurrence in pharyngeal secretions and feces of persons ill with clinical poliomyelitis Most of the reports were made before realization that the viruses occur in multiple immunologic types and represent possibly the most prevalent viral parasites of man with the possible exception of influenza viruses

Coxsackie viruses of both groups A and B are found in human excretions or secretions There have been no instances of reinfection of a single person with a single virus type and serologic evidence of development of protective type specific antibodies indicates that such a reinfection would be unlikely It has been shown however that a person may be successively infected with different immunologic types of group A virus or may simultaneously harbor two different group A types or a group A and a group B virus



Fig 4.—Extensive nodular infiltration of both lungs (Courtesy of S l w S t J A M A Arch Int Med 91 35-42 January 1953)

of two patients were only moderately increased and the count of the third was not increased Serial serologic studies although not conclusive were negative for primary atypical pneumonia psittacosis and Q fever

[An adult with chickenpox who develops pneumonia as a complication may be very ill —Ed]

COXSACKIE VIRUS INFECTIONS

Importance of Coxsackie Viruses in Human Disease, Particularly Herpangina and Epidemic Pleurodynia Robert J Huebner Edward A Beeman Roger M Cole Paul M Beigelman and Joseph A Bell[9] (Nat'l Inst of Health) discuss the 15 immunologically distinct agents of human disease known as Coxsackie viruses that were completely unknown three or

(9) New England J Med 247 49-56 Aug 14 85-89 Aug 21 1952

Outbreak of Febrile Illness Associated with Coxsackie Virus H Kenyon A D Macrae R J Dodds and J F Galpine[1] studied an outbreak of febrile illness in 52 of 75 persons in a children s home Group B strain Coxsackie virus was isolated in five cases from mouth washings and fecal specimens and neutralizing antibody appeared in the serum from the fifth day onward Not only were 21 of 25 infants infected but 6 of 9 female staff members The duration of illness varied from several days to a month Relapses after 13 31 days occurred in three cases Clinically there were headache nausea vomiting vague abdominal pain nuchal pain without rigidity occasional sternal pain sore throat and diarrhea There were no backaches Bornholm disease was ruled out by the lack of sharp chest or abdominal pain Results of cerebrospinal fluid examination in two cases were normal If the spread was from case to case the incubation period was about one week Man is probably the main reservoir and carrier of the Coxsackie virus

MUMPS

Aureomycin in Mumps LeRoy Homer and W N Donovan (U S Army Hosp Fort Knox Ky) treated 24 patients with epidemic parotitis with symptomatic measures and a similar group of 24 with aureomycin The effect of aureomycin on development of complications duration of acute febrile illness and duration of glandular swelling was evaluated No significant differences were demonstrated in the two groups with regard to duration of the febrile period of duration of glandular swelling The authors believe that the development of complications is purely fortuitous and that the occurrence of meningoencephalitis in two patients in the symptomatically treated group as compared with no such complication in the aureomycin treated group does not reflect any protective action of aureomycin This lack of ability to protect against complications is further emphasized by the fact that orchitis developed in six of the patients receiving aureomycin after they had at least 24 hours of therapy whereas in the group treated

(1) La t 153 157 J ly 6 195
( ) J A M A 150 465 467 O t 4 1952

Coxsackie viruses are widely distributed throughout the world

Because first isolations of Coxsackie viruses were made from poliomyelitis patients it has been suggested that such viruses might cause diseases resembling poliomyelitis A study of the occurrence of Coxsackie viruses including about 400 isolations from more than 7 000 specimens collected in 1949 51 and including poliomyelitis showed little basis for the hypothesis that any of the viruses encountered were producing illnesses likely to be confused with the clinical syndromes ascribed to infection with poliomyelitis virus

Coxsackie viruses are pathogenic in man The widely prevalent childhood disease known as herpangina seems to be the chief clinical manifestation of infection with many if not most group A Coxsackie viruses It is a specific febrile disease that occurs usually in epidemic form in summer and is characterized by small to minute ulcerative lesions of posterior parts of mouth and throat Zahorsky described the disease as beginning suddenly as an acute febrile attack with temperature often rising to 104 F Convulsions may occur Vomiting anorexia and prostration are sometimes marked The anterior pillar of fauces tonsils pharynx and edge of soft palate may have 2 20 minute vesicles or ulcers Dysphagia is often marked General and local symptoms disappear in a few days Prognosis is favorable and treatment symptomatic

Epidemic pleurodynia is also caused by Coxsackie viruses This alarming but nonfatal disease occurs in both epidemic and endemic form and has been reported from all parts of the world It is characterized by sudden onset of abdominal or chest pain fever headache and anorexia with associated respiratory distress Invariably all patients recover but relapses and complications occur and convalescence may be prolonged Clinical diagnosis of the disease in sporadic suspected cases is however difficult if not impossible It may simulate appendicitis common duct obstruction pancreatitis coronary occlusion pneumonia pleurisy and intestinal infection Epidemic pleurodynia is caused by one or more of the group B Coxsackie viruses

[Here is an excellent statement on the present state of knowledge of th Coxsackie group of viru es —Ed]

of hepatitis to 4 700 Danish doctors practically all the nation s physicians and received 4 458 responses All 2 000 Danish lawyers were sent a similar questionnaire with 1 862 responses A group of nurses and 2 190 industrial workers were also questioned

Hepatitis before age 18 occurred in the professional groups to the same extent (about 8%) but in only 4% of the workers Of hepatitis occurring after age 18 doctors in all age groups had a higher incidence reaching 12% in doctors questioned at age 40-50 The incidence in nurses and lawyers is lower and similar The maximal frequency for doctors and lawyers *is in age group 40 50 for the other groups of persons the* maximum is in age group 30-40 It is interesting that during World War II there were four to seven times as many cases of hepatitis among officers as among privates Both doctors and lawyers report that the disease occurred most often at age 25 30

When the figures are corrected for the age of the sample and the death rate it is found that whereas in the 1930 s hepatitis most frequently attacked children in the 1940 s it became a predominantly adult disease showing the same change as observed in poliomyelitis It is remarkable that nurses who are also in close contact with infectious patients feces and urine do not show the same supermorbidity as doc tors One must seek other sources of infection for doctors and the great importance of inoculation hepatitis has been stressed These findings confirm similar studies in Sweden which demonstrated a supermorbidity among hospital doctors as compared with general practitioners and surgeons

Murray Valley Encephalitis Frank MacFarlane Burnet[5] (Royal Melbourne Hosp) believes that the nature of the Aus tralian X disease epidemics of 1917 and 1918 has now been solved From January to March 1951 a small epidemic of precisely similar character to that of 1917 18 occurred in Northern Victoria From patients who died a virus was iso lated which has been shown by French and Miles to behave in experimental animals like that transferred to monkeys and sheep in 1918 by Cleland Bradley and Campbell This virus is called Murray Valley encephalitis virus and the type strain has been studied by American workers It clearly falls into

(5) Am J P b H lth 42 1519 1521 D mbe 195

symptomatically five patients had orchitis after 24 hours of hospitalization including the two patients with meningo encephalitis

The authors were unable to demonstrate that aureomycin had any beneficial effect in epidemic parotitis or its com plications

[The evidence is now conclusive that presently available antibiotics do not affect the course of mumps—Ed]

Mumps Arthritis Emanuel Appelbaum Jerome Kohn Ruth E Steinman and Martin A Shearn[3] (New York Univ Post Grad Med School) report four cases of mumps compli cated by arthritis of which the following is typical

Man 40 was hospitalized with bilateral parotic swelling of five days duration He did not appear acutely ill but had testicular pain fever and tenderness in the right upper quadrant Aspirin was given and an ice bag applied to the scrotum On the third day he had nausea headache and high fever without any neurologic signs Diethylstilbestrol 15 mg daily given for four days caused consid erable improvement On the ninth day pain and tenderness of the posterior aspect of the left leg appeared followed by edema redness and tenderness of the left ankle with severe limitation of motion The left knee became warm and tender Temperature was 102 F ACTH was given intravenously for five days starting with 20 mg and reducing to 10 then 5 mg with dramatic improvement He relapsed two days after ACTH was stopped but responded promptly to a second six day course with relief and euphoria Three weeks after discharge he was able to walk without difficulty

It is possible that mumps arthritis is due to an antigen antibody reaction similar to the mechanism proposed for the poststreptococcic diseases since 10 14 days usually elapsed from the onset of mumps to the appearance of arthritis Mumps arthritis has no clinical features distinguishing it from other forms of infectious arthritis usually taking the form of migrating polyarthritis involving both large and small joints and sometimes accompanied by tenosynovitis or collec tions of synovial fluid

[Another common viral infection in which arthritis occurs occasionally is rubella —Ed]

MISCELLANEOUS VIRAL INFECTIONS

Frequency of Hepatitis in Doctors Sten Madsen[4] (Finsen Inst Copenhagen) sent questionnaires regarding the incidence

(3) A M A A h I t Med 90 17 3 A gu t 1952
(4) P stg ad Med 11 517 522 J 1952

of hepatitis to 4 700 Danish doctors practically all the nation s physicians and received 4 458 responses All 2 000 Danish lawyers were sent a similar questionnaire with 1 862 responses A group of nurses and 2 190 industrial workers were also questioned

Hepatitis before age 18 occurred in the professional groups to the same extent (about 8%) but in only 4% of the workers Of hepatitis occurring after age 18 doctors in all age groups had a higher incidence reaching 12% in doctors questioned at age 40 50 The incidence in nurses and lawyers is lower and similar The maximal frequency for doctors and lawyers is in age group 40 50 for the other groups of persons the maximum is in age group 30-40 It is interesting that during World War II there were four to seven times as many cases of hepatitis among officers as among privates Both doctors and lawyers report that the disease occurred most often at age 25 30

When the figures are corrected for the age of the sample and the death rate it is found that whereas in the 1930 s hepatitis most frequently attacked children in the 1940 s it became a predominantly adult disease showing the same change as observed in poliomyelitis It is remarkable that nurses who are also in close contact with infectious patients feces and urine do not show the same supermorbidity as doc tors One must seek other sources of infection for doctors and the great importance of inoculation hepatitis has been stressed These findings confirm similar studies in Sweden which demonstrated a supermorbidity among hospital doctors as compared with general practitioners and surgeons

Murray Valley Encephalitis Frank MacFarlane Burnet[5] (Royal Melbourne Hosp) believes that the nature of the Aus tralian X disease epidemics of 1917 and 1918 has now been solved From January to March 1951 a small epidemic of precisely similar character to that of 1917 18 occurred in Northern Victoria From patients who died a virus was iso lated which has been shown by French and Miles to behave in experimental animals like that transferred to monkeys and sheep in 1918 by Cleland Bradley and Campbell This virus is called Murray Valley encephalitis virus and the type strain has been studied by American workers It clearly falls into

(5) Am J P b H alth 42 1519 1521 Dec mbe 1952

symptomatically five patients had orchitis after 24 hours of hospitalization including the two patients with meningo encephalitis

The authors were unable to demonstrate that aureomycin had any beneficial effect in epidemic parotitis or its com plications

[The evidence is now conclusive that presently available antibiotics do not affect the course of mumps —Ed]

Mumps Arthritis Emanuel Appelbaum Jerome Kohn Ruth E Steinman and Martin A Shearn[3] (New York Univ Post Grad Med School) report four cases of mumps compli cated by arthritis of which the following is typical

Man 40 was hospitalized with bilateral parotic swelling of five days duration He did not appear acutely ill but had testicular pain fever and tenderness in the right upper quadrant Aspirin was given and an ice bag applied to the scrotum On the third day he had nausea headache and high fever without any neurologic signs Diethylstilbestrol 15 mg daily given for four days caused consid erable improvement On the ninth day pain and tenderness of the posterior aspect of the left leg appeared followed by edema redness and tenderness of the left ankle with severe limitation of motion The left knee became warm and tender Temperature was 102 F ACTH was given intravenously for five days starting with 20 mg and reducing to 10 then 5 mg with dramatic improvement He relapsed two days after ACTH was stopped but responded promptly to a second six day course with relief and euphoria Three weeks after discharge he was able to walk without difficulty

It is possible that mumps arthritis is due to an antigen antibody reaction similar to the mechanism proposed for the poststreptococcic diseases since 10 14 days usually elapsed from the onset of mumps to the appearance of arthritis Mumps arthritis has no clinical features distinguishing it from other forms of infectious arthritis usually taking the form of migrating polyarthritis involving both large and small joints and sometimes accompanied by tenosynovitis or collec tions of synovial fluid

[Another common viral infection in which arthritis occurs occasionally is rubella —Ed]

MISCELLANEOUS VIRAL INFECTIONS

Frequency of Hepatitis in Doctors Sten Madsen[4] (Finsen Inst Copenhagen) sent questionnaires regarding the incidence

(3) A M A Arch Int Med 90 217 3 August 1952
(4) I tgr d M d 11 517 5 2 J 195

complicating meningococcic infections is well known. Vaccinia as well as the herpes simplex virus may produce a clinical picture similar to that described by Kaposi as a varicelliform eruption (eczema herpetiforme).

Girl, 7, was drowsy and lethargic on awakening one morning. By afternoon she had fever, was delirious and had a skin rash. On hospitalization she was comatose with fever of 106 F, fresh petechial hemorrhages in the skin and mucous membranes, subconjunctival hemorrhages, slight nuchal rigidity and a Kernig sign. She had had infantile eczema from age 4–14 months, after which skin lesions had not recurred. White cell count was 4,200 and blood culture revealed Neisseria meningitidis (intracellularis). Spinal fluid showed 25 mononuclear cells/cu mm, glucose 100 mg and protein 25 mg/100 cc and chloride 126 mEq/L; the culture was sterile. She was given 1 Gm sodium sulfadiazine intravenously and 1 Gm subcutaneously on hospitalization and 1 Gm every six hours thereafter; she also received 30,000 units of penicillin every three hours. The next day there was more evidence of meningitis but no longer delirious, she became rational and alert within 36 hours.

Two days after hospitalization she had typical vesicular rash of herpes labialis. The following day the vesicular lesions on an erythematous base had become disseminated over much of the body and involved both dorsal and flexor surfaces of the elbows and knees (Fig 5) as well as buttocks and thighs. The lesions continued to spread for the next 72 hours, then spontaneously subsided. At no time did the eruption seem to cause any significant discomfort. The subsequent course was uneventful. At no time during the observation period were eczematoid lesions seen. Herpes simplex virus was isolated from the vesicle contents.

It should be noted that the generalized eruption caused by herpes simplex occurred on an apparently intact skin. Ordinarily such eruptions occur on a skin that is presumably rendered more susceptible by another disease, usually infantile eczema.

Herpes Zoster is discussed by Pearce Bailey[7] (Georgetown Univ.). The etiologic agent is generally conceded to be a specific virus that is distinct from the virus causing herpes febrilis but closely related to the virus of varicella. Herpes zoster has the features of an infective disease. Malaise and fever often precede the characteristic neurologic and cutaneous signs. One attack confers almost complete immunity. The disease tends to have a seasonal variance, being more common in spring and fall, and is contagious.

The cardinal clinical manifestations of spinal zoster are

(7) [illegible] 12:123-13[illegible], Aug. 1952.

the Japanese B St Louis West Nile group of mosquito borne encephalitis viruses and appears to have a status equivalent to that of each of the other three

It is only just to claim for Cleland Bradley and Campbell the first recognition of a disease of the type now called insect borne encephalitides and the first isolation of one of the viruses responsible In 1918 Cleland and his collaborators showed that brain material from patients who died could induce a fatal transmissible encephalitis on intracerebral inoculation in monkeys and sheep This was before the days of the mouse and chick embryo and before means of preserving and transporting viruses had been developed Published accounts of their experiments and examination of histologic material indicate that their findings are identical with those of recent studies of the disease

Generalized Cutaneous Herpes Simplex Report of Case Complicating Meningococcemia According to Laurence Finberg and Robert S Easton[6] (Baltimore City Hosp) localized herpes simplex infection in the form of herpes labialis



Fig 5 —Cl e p l g d t l of th f (Court y f F b g L nd E t R S J P d t 41 188 191 A gu t 1952)

(6) J P d t 41 188 191 Augu t 1952

ocular complications In about 50% of cases ophthalmic zoster extends to the globe of the eye causing disturbances in the transparent media iris sclera cornea optic nerve or muscles

In geniculate zoster or Hunt s syndrome the vesicles are found on the auricle and less frequently on the anterior pillar of the fauces There is pain in the ear and mastoid region radiating to the anterior pillar of the fauces and to the vertex Involvement of the chorda tympani results in taste loss in the anterior two thirds of the tongue on the homolateral side There is almost always facial paralysis often associated with clonic facial spasm

In all patients with herpes zoster mechanical and chemical injury toxic and infectious diseases and tumors of the cord must be ruled out

There is no specific treatment The application of calamine lotion is usually sufficient for skin lesions in the average case of spinal zoster Aureomycin may be used orally and locally for ophthalmic zoster The advice of an ophthalmologist is essential because of the dangers to vision Pain is usually easily controlled but the problem presented by extreme cases of postherpetic neuralgia is still unsolved

There is a current trend to distin uish between acute herpetic and postherpetic pain on neurophysiologic grounds The tendency is to regard postherpetic pain as a reactive vicious cycle type caused by activation of self contained pain circuits in and above the thalamus Bucy theorizes that these circuits between the thalamus and cortical areas are activated and perpetuated by a lowered threshold at synapses due to hypoxia attendant on cerebral arteriosclerosis These theories form the background for use of frontal lobotomy and topec tomy in cases of intractable postherpetic neuralgia There has been some reported relief after lobotomy manifested by a change in the patient s attitude toward the pain but not by elimination of the pain itself

Studies of Rubella Immunization 1 Demonstration of Rubella without Rash Saul Krugman Robert Ward Kathryn Giblin Jacobs and Martin Lazar[8] (New York Univ Bellevue Med Center) found that nasopharyngeal washings and blood obtained from patients with rubella on the first day of rash and from the blood in one patient two days before the rash

(8) J A M A 151 285 288 J n 24 1953

radicular pain and paresthesias and cutaneous eruptions in the corresponding dermatomes The thoracic segments are most commonly involved The disease is especially common in persons who are overworked or ill Pain usually appears where the rash later develops It varies from aching and soreness to pain of great intensity variously described as burning gnawing shooting stabbing or neuralgic The initial pain and paresthesias tend to abate when the vesicles appear The cutaneous eruptions which in the average case develop about four days after onset of symptoms begin as a patchy erythema with edema of the skin The characteristic cluster of vesicles containing clear fluid then appears usually in a patch of erythema The clusters tend to develop and spread where the posterior primary ramus and the lateral and anterior branches of the anterior ramus come to the surface The vesicular band following radicular lines runs transversely around the trunk and vertically over the arm or leg The vesicular groups seldom occupy the entire dermatome its limits being better delineated by the erythema The lesions are almost always unilateral In the average case the vesicles soon subside dry up scab over and in 7 or 10 days desquamate leaving either shallow brown scars or faint marks that are difficult to trace

Motor disturbances are rare only 44 instances having been reported in the literature up to 1943 Complete recovery from motor involvement occurs in only about 15% of cases and requires six months to one year In the other cases there are residual atrophy and weakness The cerebrospinal fluid is abnormal in about 40% of cases pleocytosis and increased protein content being the predominant features

Most patients with spinal zoster recover without incident within 10 days to 3 weeks and present no special therapeutic problem

Postherpetic neuralgia occurs mostly in the aged with signs of arteriosclerosis It begins a few weeks after termination of the acute stage and is characterized by continuing pains rising on occasion to paroxysms of intolerable sensation which may persist for months or years It may lead to depression and even suicide

The commonest form of zoster next to thoracic involvement is ophthalmic zoster It is prone to be followed by a painful postherpetic syndrome and may give rise to dangerous

common Usually only one eye was involved The infection did not cause any time loss from work

Specimens were obtained from 10 patients with acute cases by rubbing a cotton swab over the conjunctiva and placing the swab in 10% horse serum in broth and frozen Newcastle virus was isolated from four specimens There were no significant serologic changes in paired serum specimens from acute and convalescent cases These 40 cases may be added to 8 previously reported and are of special interest since only 2 of the previous 8 occurred naturally

Neurologic Complications Following Antirabies Vaccination. Emanuel Appelbaum Morris Greenberg and Jack Nelson[1] (New York City Dept of Health) report 46 cases of encephalomyelitis or neuritis after injection of phenolized (Semple) vaccine from 1928 to 1951 The cause of the encephalomyelitis that appears after antirabies vaccination is not clear The paralytic accident usually occurred within 8 21 days of the initial injection of the vaccine The shortest interval between the injection and the onset of neurologic involvement was 6 days the longest 45 The onset was usually sudden with chills varying grades of fever headache vomiting and changes in mental state There are three clinical types The encephalitic type was usually characterized by fever headache pains in the body and extremities changes in the mental state and nuchal rigidity associated with Brudzinski and Kernig signs changes in deep and superficial reflexes and disturbances in bladder function There were 37 patients in this group Onset of the dorsolumbar myelitic type was more gradual Patients complained of back pain followed in a few hours or days by leg paralysis partial or complete anesthesia and loss of sphincter control Two of the five patients in this group had flaccid paralysis with abolition of the reflexes In the neuritic type mainly the peripheral nerves were involved Two of four patients in this group had sensory disturbances in all extremities but no muscle weakness one had weakness associated with sensory symptoms and absence of reflexes in all four extremities and one had footdrop

Spinal tap in 33 patients revealed clear fluid in most instances and somewhat increased pressure a moderate increase in the number of white cells was the commonest abnor

(1) J A M A 151 188 191 Jan 17 1953

appeared could produce typical rubella when injected into noses and throats of susceptible persons The incubation period for induced rubella ranged from 9 to 16 days The course of the experimental disease and the character and distribution of the rash in no way differed from naturally acquired rubella The illness was extremely mild causing much less discomfort than the common cold Experimental rubella was contagious it produced the typical disease in susceptible persons after natural exposure Attempts to transfer the agent to cynomolgus monkeys were unsuccessful

The same causative agent that produced typical rubella with rash also produced rubella without rash The phenomenon of rubella without rash has been suspected on epidemiologic grounds for many decades but these experiments are the first direct proof of its occurrence

The agent could be preserved in the dry ice chest at —70 C for at least nine months

The study may point the way toward practical methods of deliberate infection and active immunization of girls before the childbearing period There are definite hazards connected with this procedure The evidence that experimental rubella is as contagious as naturally acquired rubella indicates that the uncontrolled introduction of this disease into the community may possibly increase the danger to pregnant women

[It certainly appears desirable that females acquire rubella in childhood These workers are developing methods which would make feasible the deliberate inoculation of young girls —Ed]

Outbreak of Conjunctivitis Due to Newcastle Disease Virus (NDV) Occurring in Poultry Workers C B Nelson B S Pomeroy Katherine Schrall W E Park and R J Lindeman[9] (Minnesota Dept of Health and Univ of Minnesota) report 40 cases of conjunctivitis occurring in spring 1951 in workers in a produce plant where poultry is eviscerated processed and canned Most of the 90 workers on the eviscerating line were women One male worker had the disease Symptoms lasting three or four days consisted of irritation of the involved eye lacrimation redness and some swelling of the conjunctiva but no involvement of the cornea edema of the lids was present in varying degree Preauricular adenitis on the affected side was present in about half the cases No constitutional symptoms were noted and headache was un-

(9) Am J P b H lth 4 672 678 J n 1952

CAT SCRATCH DISEASE

Cat Scratch Disease Nonbacterial Regional Lymphadenitis Worth B Daniels and Frank G MacMurray[2] (Washington D C) analyzed 60 cases Males and females were affected equally Most of the patients were under age 20 and a third under age 10 All except five had had contact with cats and these could not recall an exposure Thirty three had a history of scratch in the region drained by the affected node or nodes For 14 patients the exact mode of inoculation was unknown Seven small household epidemics involving 16 persons were studied Each outbreak has centered about the family cat All cats implicated were healthy Evidence seems to indicate that these animals probably transmit the disease only passively ince they have negative intradermal reactions to cat scratch antigen

Several types of primary lesions were observed There were seven inflamed scratches inflammation being present along the whole length in some instances and at only one site in others Other lesions were covered with a scab under which a small amount of exudate could be expressed The primary lesion in some cases was a raised purple or dusky red scar In 13 there were red papules some resembling small furuncles and others insect bites (Fig 6) Six patients had a single ulcer one had two purple fang marks and one had a papule surmounted by a vesicle

The axillary nodes were involved in 35 cases the epitrochlear nodes in 10 and the head and neck nodes in 17 The nodes were often striking in size and in some cases were rubbery and nontender More often they were tender with redness heat and swelling of the overlying skin Malaise anorexia nausea weakness lassitude aching chills or chilly sensations and headache occurred in two thirds of the patients Six had a rash for about 48 hours One had pinpoint papules on the upper trunk another had an erythematous maculopapular eruption on the thumb and index finger of both hands and four had an eruption resembling measles Fever which occurred in two thirds of the patients lasted from three days to

(2) A I t. Med 37 697 713 Octob 1952

mality The highest cell count was 1 260 Differential count revealed definite predominance of lymphocytes in all but two patients The sugar level was normal or elevated in all patients tested Cultures of cerebrospinal fluid specimens were uniformly sterile

Recovery usually took one or two weeks There were no deaths Of 45 patients followed up 29 recovered completely and 16 had some residual condition but neurologic complications were never severe enough to prevent the person from resuming his normal occupation

The risk of rabies from a bite by a rabid animal is greater than that of postvaccinal encephalomyelitis Of 707 persons bitten by rabid animals in New York City from 1935 to 1948 all but 8 took antirabies treatment All six cases of human rabies in this period were fatal only two of the patients had received antirabies vaccine Mortality for patients treated with Semple vaccine was 0 3% It is estimated that 5 15% of persons bitten by rabid animals get rabies Treatment in this series therefore saved 35 106 human lives In the same period there were 41 cases of postvaccinal encephalomyelitis All of the patients survived and most of them recovered completely Treatment was apparently worth the risk

Antirabies vaccination should be reserved for persons definitely bitten by rabid animals and not for those who have played with touched or been scratched by the animal

The New York City Department of Health advises antirabies vaccination only after a bite by a rabid animal by a suspected rabid animal until its status has been established or by a stray dog that cannot be apprehended Known dogs or cats that bite human beings are observed for one to two weeks and unless rabies appears in them no treatment is advised Treatment is not advised after bites by squirrels rats or other animals since rabies has not been found among them in the city

[The figures given are reassuring especially the fact that there were no deaths Deaths have occurred in other series of cases however Nevertheless on the basis of these figures one would feel less reluctant to give antirabies vaccine treatment for a person who had been bitten by a rabid animal —Ed.]

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five weeks and was usually mild In general there were more fevers of short duration in the nonsuppurative group

All patients had a positive reaction to intradermal tests with the cat scratch antigen which is prepared in the same way as the original Frei test antigen

In 41 cases the leukocyte count was equally divided be



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tween those above and those below 10 000 cu mm Cultures of pus from nodes on ordinary mediums performed in 19 cases were all sterile

The axillary type of disease often confused with tularemia was most commonly encountered The cervical form which may simulate Hodgkin s disease lymphosarcoma infectious mononucleosis or tuberculous adenitis is the next most fre

quent The disease may be confused with lymphogranuloma venereum Parinaud s oculoglandular syndrome can be caused by cat scratch disease Encephalitis in a child with concurrent suppurative disease of the axillary nodes has been reported

Sulfonamides and antibiotics have been used therapeuti cally but there is no evidence that any of these drugs pro duced cure

This report on 60 cases indicates that the di ease is fre quent and widespread in America and often unrecognized It can be confused with many diseases of the lymph nodes It is important that pathologists be cognizant of the lymph node findings since though the microscopic picture is not diag nostic it is characteristic enough to suggest the probable diagnosis which can then be confirmed by intradermal testing

[This is th work which called attent n to th common occurrence of the d sease in America Everyone who looks for it seems to find it presumably many of these cases had passed under such diagno e as non specific lymphadenitis The main importance of know ng of it is to prevent confusion with entities having a more serious prognosis such as tubercu losis or neoplastic di ease (See next article)—Ed]

Cat Scratch Disease Simulating Sarcoma of Neck A typ ical case of cat scratch disease is characterized by an initial cutaneous lesion at the site of a skin injury or cat scratch followed in a few days by regional lymphadenitis which often proceeds to suppuration with sterile pus A primary lesion which develops in about half the patients consists of a slightly raised purple papule or plaque surmounted by a vesicle pustule or scab Regional lymph adenopathy most commonly develops about three weeks after the scratch The serum of many pa tients gives a positive complement fixation reaction with the virus of lymphogranuloma venereum This suggests a certain antigenic similarity between the two etiologic agents There is no cross reaction between the two diseases as regards the skin test

The disease may simulate a variety of other conditions The epitrochlear and axillary form resembles ulceroglandular tularemia The cervical form resembles tuberculous cervical adenitis when suppurative and infectious mononucleosis lymphosarcoma or Hodgkin s disease when nonsuppurative The femoroinguinal form simulates lymphogranuloma ve nereum

Frank G MacMurray Marshall C Sanford and Theodore Winship[3] (Washington D C) report an unusual case in which

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the correct diagnosis was not at first suspected because the clinical features were completely atypical

Girl 4 for 10 days had had a small firm fixed nontender lump in the suprasternal notch General physicians who saw the child thought the mass was malignant and suggested surgical removal The child was afebrile and the mass which measured about 2 5 ×1 5 cm was easily palpable The cervical nodes were not enlarged The preoperative impression was chondrosarcoma of the sternoclavicular joint The mass was removed together with a nearby lymph node Pathologic study revealed inflammatory changes in the lymph nodes compatible with cat scratch disease Giemsa stains showed small dark red inclusion bodies in histiocytes similar to those described by *Mollaret and co workers*

An intradermal test with cat scratch disease antigen produced a strongly positive reaction in 48 hours The patient s mother then stated that the patient was often scratched by two kittens and that there had been a maculopapule resembling an insect bite on the right side of the child s chin 10 days before the suprasternal mass was discovered It was found that the child s sister had had a more typical case at that time with a tender enlarged submandibular lymph node malaise and fever She had a strongly positive reaction to the intradermal test

Atypical Forms of So called Cat Scratch Disease (Benign Virus Lymphadenitis) are reported by C Usteri T Wegmann and Chr Hedinger[4] (Univ of Zurich) In typical cases with *regional lymphadenitis the most significant symptom infection* is transmitted not only by cat scratches but also by other injuries (e g insect bites thorns and the like) The increasing number of observations shows that apart from cutaneous in*fections enteral bronchogenic and other portals of entry* may exist and that there are typical and atypical forms of the disease Some of the atypical forms can only be explained by assuming a noncutaneous portal of entry

*Typical forms of cat scratch disease (CSD) include glandu*lar cutaneous and mixed types of which the glandular type is well enough known In the cutaneous form seen mostly by dermatologists the cutaneous portal of entry or primary lesion is a papule *an ulceration or a small scab which at the time* of florid lymphadenitis has mostly disappeared In rare instances however the cutaneous lesion is predominant the lymphadenitis less noticeable and only intracutaneous skin tests with CSD antigen make *differential diagnosis possible* against various sorts of primary lesions (syphilis tuberculosis Bang s disease mycosis and the like) because neither clin

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ical nor histologic appearance are per se characteristic in CSD It was recently noticed that typical forms of CSD are clin ically and microscopically very similar to skin manifestations after BCG inoculation

Atypical forms include so called pseudovenereal erythema nodosum like ocular anginous mesenteric pulmonary and meningoencephalic types The so called pseudovenereal type reported mostly by French authors includes cases which be cause of a more or less florid lymphadenitis inguinalis were suspected of being venereal disease Examinations of genital organs and the blood did not reveal venereal disease In an other group mostly children the clinical appearance was one of inguinal or femoral hernia There is one observation only of the erythema nodosum like type tuberculin tests were negative skin tests with CSD antigen positive Three mem bers of the family showed lymphadenitis the result of in juries by cat s claws The ocular type can be subdivided into a pseudooculoglandular form with primary lesion in the cutaneous part of the eyelid and noninvolvement of the con junctiva and the oculoglandular form in which conjuncti vitis predominates and infection is assumed to occur by way of the conjunctival mucus membrane In the second group tularemia must be excluded It might be well to remember that infections with the Newcastle virus in man may produce simi lar clinical manifestations and that probably one case or an other of the Parinaud syndrome might be caused by CSD infection So far only two cases of the anginous type have been seen The symptoms consisted of unilateral febrile an gina with pharyngeal abscess and suppurative lymphadenitis in one case therapy resistant tonsillitis arthralgia and lym phadenitis in the other Results of intracutaneous tests with CSD antigen were positive in both observations The authors report three cases of the mesenteric type all in young pa tients operated on for suspected appendicitis The appendixes were however normal and large lymph nodes resembling tuberculous mesenteric lymph nodes were found in the mesentery Results of tuberculin tests were negative CSD anti gen tests positive Microscopic examination of lymph nodes re vealed changes similar to those found in typical CSD but necrosis was more extensive and tuberculoid structures less pronounced Infection through the mucus membrane is as sumed for this type which is described for the first time

Whether pulmonary and meningoencephalic types exist is open to discussion Two cases are reported one of atypical pneumonia another of lymphocytic meningitis both yielded positive skin reactions to CSD antigen the only indication of possible CSD infection Since skin tests may however remain positive for a long time even years after an attack of cat scratch disease (anamnestic reaction) the triad of clinical and histologic appearance and positive intracutaneous reactions to CSD antigen is conclusive

[This is a particularly interesting paper Perhaps the authors are a little too enthusiastic about extending the clinical potentialities of cat scratch disease on the other hand it seems entirely reasonable to suppo e that the responsible agent can cause some of these other syndromes Mesenteric lymphadenitis is certainly worth investigating from this stand point —Ed]

COLLAGEN DISEASES

Incidence and Etiologic Background of Chronic Biologic False Positive Reactions in Serologic Tests for Syphilis Preliminary Report is presented by Joseph Earle Moore and Charles F Mohr (Johns Hopkins Univ) Biologic false positive (BFP) reactors may be divided into acute and chronic Acute BFP reactions are due to a large number of infections bacterial viral plasmodial rickettsial or protozoal They appear during or immediately after such a precipitating infectious cause and regress spontaneously to normal within a brief period not exceeding six months Chronic BFP reactions are characterized by absence of the commonly known precipitating causes of acute reactions and persist for years

The existence of a treponemal immobilizing (TPI) antibody in syphilis and other treponematoses and its separate identity from reagin has been demonstrated by Nelson and Mayer Published studies indicate that the TPI antibody does not occur in normal persons or in patients with nonsyphilitic diseases but appears with regularity in persons with untreated syphilis and related treponematoses Tests indicated that the antibody usually disappears from the serum of persons with treated early syphilis but rarely from that of persons whose original treatment was for late syphilis instead it persists for a lifetime The following interpretation may be placed on various combinations of standard TPI and STS (serologic test

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for syphilis) results A patient with both TPI and STS positive reaction has syphilis whether treated or untreated a patient with a negative STS and a positive TPI reaction has syphilis and a patient with a negative TPI and a positive STS reaction is practically always a BFP reactor

A group of 300 patients who were routinely discovered to have positive STS reactions in the absence of any clinical evidence of syphilis was studied Latent syphilis was diagnosed in 54% on the basis of positive TPI reactions and 46% were diagnosed as BFP reactors This indicates that nearly half the positive standard STS reactions discovered in routine blood testing do not represent syphilis but instead indicate BFP reactions

Little is known of the cause of chronic BFP reactions The only identified infection is leprosy in which the incidence of BFP reactions is variously reported to be 40 60% This disease did not cause any of the chronic BFP reactions in the 300 cases The only other chronic disease so far suggested as a frequent cause of BFP reactions is discoid or disseminated lupus erythematosus The incidence of BFP reactions in various series of patients ranged from 5 to 30% or more

Plans have been set up to restudy a group of chronic BFP reactors over a period of years Laboratory routine includes a complete hemogram urinalysis total blood protein determinations albumin globulin ratio cephalin flocculation and thymol turbidity tests a search for L E cells in the peripheral blood and other laboratory and x ray studies as indicated Of 51 patients who completed at least one detailed re examination all but 6 had some significant abnormality other than the BFP reaction Five had proved collagen disease (disseminated lupus erythematosus in four rheumatoid arthritis in one) One patient each had sarcoid Hodgkin s disease and Gaucher s disease Probable diagnosis for 23 others was collagen disease (21) and sarcoid (2) Many laboratory abnormalities such as elevated sedimentation rate positive cephalin flocculation and thymol turbidity elevated serum globulin level proteinuria and cylindruria were found in 14

A complete study of BFP reactors will provide an opportunity to define the early manifestations and natural history of the collagen disease group

[1] As brought out in the paper the treponemal immobilizing antibody

test has been of utmost value in study of patients suspected of having biologic false positive results in tests for syphilis It appears that a chronically false positive result in serologic tests for syphilis should be looked upon as indicative of serious underlying disease As shown here and in the next paper lupus erythematosus is especially to be suspected —Ed]

Systemic Lupus Erythematosus Preceded by False Positive Serologic Tests for Syphilis Presentation of Five Cases is made by John R Haserick and Roland Long[6] (Cleveland Clinic) Biologic false positive results of serologic tests for syphilis have frequently been observed in patients with all types of lupus erythematosus The time factor between development of serologic alterations and onset of clinical manifestations of lupus erythematosus is unknown No previously reported cases were found in which false positive results of tests for syphilis were observed before clinical manifestations of lupus erythematosus

Of 29 patients with systemic lupus erythematosus 7 had had positive tests for syphilis Five of the seven positive results had been noted one to seven years before first symptoms of systemic lupus erythematosus appeared

CASE 1 —Woman 24 had a false positive reaction for syphilis in 1943 three years before appearance of first signs of lupus Results of plasma L E test in 1949 were positive Autopsy confirmed diagnosis of systemic lupus

CASE 2 —Three years before onset of clinical lupus woman 34 had had persistent weak positive results of serologic tests for syphilis and had been treated for latent syphilis She suffered severe psychic trauma

CASE 3 —Woman 25 had a false positive reaction for syphilis in a premarital examination eight years before appearance of recognizable signs and symptoms of systemic lupus Diagnosis of syphilis resulted in severe reactive depression Wassermann and Kahn titers increased with onset of clinical manifestations of lupus

CASE 4 —Woman 41 had had a false positive reaction for syphilis almost two years before she showed early symptoms of lupus and five years before she entered the acute phase of the disease

CASE 5 —Woman 24 had had false positive reactions for syphilis shortly before early symptoms of lupus appeared and four years before a severe attack of the disease False positive results led to unnecessary treatment for nonexistent syphilis

Montgomery and McCreight found that serologic tests for syphilis yielded positive results in 44% of cases of acute disseminated lupus erythematosus Rein and Kostant found that 35% of patients with lupus had positive results of serologic

(6) A I t M d 37 559 565 S ptembe 195

tests for syphilis and Coburn and Moore found that 11 of 30 patients with lupus had positive Wassermann reactions More specific plasma alterations have been discovered through investigations into the L E factor which is responsible for the entire lupus erythematosus phenomenon noted first in the patient s own bone marrow The plasma L E test provides a valuable and accurate indicator of systemic lupus erythematosus In some cases the plasma L E test results are positive when the clinical course is mild and atypical and diagnosis of systemic lupus erythematosus is considered remote The plasma L E test results and the false positive serologic reactions wax and wane with the clinical course

Pathogenesis of lupus erythematosus is unknown The present study suggests that false positive results of serologic tests for syphilis may in some cases be the first indication of lupus erythematosus occurring before outbreak of clinical symptoms A diathesis for lupus erythematosus is thus suggested This concept is supported by previously reported cases of epilepsy in lupus erythematosus in which convulsive seizures were noted in two patients for years before onset of lupus erythematosus symptoms

Dermatomyositis and Malignant Neoplasm Brunner and Lobriaco (1951) collected 17 cases and added 1 of their own of dermatomyositis associated with malignant neoplasms Charles E Cottel[7] (V A Hosp Portland Ore) reports two cases of dermatomyositis with malignancy in which the initial complaints were due to the collagen disease

Case 1—Man 50 had a mild erythematou scaling rash on the head neck and dorsum of the hands Pain soreness and weakness of the muscles appeared later The rash became more severe and there was periorbital edema Severe tenderness and weakness of the paraspinal and shoulder girdle muscle developed and the overlying skin was warm firm and edematous An epigastric mass was found and an upper gastrointestinal series revealed carcinoma of the stomach The carcinoma was re ected but he died shortly thereafter Autopsy revealed diffuse d rmatomyositis

Case 2—Man 58 complained of generalized muscle pain weakness and swelling of the hands face and leg Periorbital edema appeared later Acute dermatomyositis was diagnosed after generalized edema and muscle tenderne s were noted The downhill course was rapid Autopsy revealed diffuse dermatomyositis and a clear cell adenocarcinoma of the left kidney

(7) Am J M S 2 4 160 168 A g t 1952

There may be a possible causal relationship between tumors and some dermatomyositis

[This association is one we should keep in mind A patient with dermatomyositis like one with acanthosis nigricans should be studied with utmost care for the presence of neoplasm somewhere —Ed]

DISEASES OF UNCERTAIN ETIOLOGY

Clinical and Laboratory Study of 31 Patients with Hemorrhagic Fever Giulio J Barbero Sidney Katz Henry Kraus and Charles L Leedham[8] report on an outbreak of epidemic hemorrhagic fever during the autumn of 1951 and the winter of 1951 52 along the 38th parallel of Korea chiefly in and around the cities of Kumhwa Chorwon and Yonchon Studies were carried out on 31 patients United Nations personnel from that area Histories of food and water ingestion individual activities disease contacts or past illnesses offered no etiologic clue

The clinical syndrome was a composite of nonspecific febrile cardiovascular gastrointestinal renal and hemorrhagic manifestations with occasional neurologic complications Onset was usually abrupt with shaking chills fever headache backache dizziness eye pain and blurred vision In the first few days malaise fatigue anorexia nausea vomiting and myalgia were added Almost from the onset there was a deep erythematous flush of the neck and face injection of the membranes of the soft palate and palpebral conjunctiva and edema of the face and eyelids Examination revealed abdominal tenderness costovertebral angle tenderness moderate lymphadenopathy and occasional enlargement of liver or spleen During the acute febrile period the patient showed signs of peripheral vascular collapse with hypotension and weak peripheral pulses Usually all symptoms and signs become most intense between the third and seventh days

As early as the second day a hemorrhagic tendency was evidenced by petechiae in the axillae and soft palate These and other signs of hemorrhage reached their height at the end of the first week During the period of hemorrhage capillary fragility increased platelets decreased in number and bleeding time was prolonged

(8) A I A A k Int M d 91 177 196 F b y 1953

Renal involvement appeared between the second and fourth days of illness with microscopic hematuria and albuminuria Clinically the renal aspect resembled lower nephron nephrosis By the end of the first week the urine output began to decline reaching the lowest volumes early in the second week Along with the oliguria the specific gravity fell to low values and blood nitrogen retention appeared The renal damage varied from transient abnormalities of the urine to severe uremia

Toward the end of the second week many of the symptoms began to subside Fever was diminished Hemorrhages appeared with decreasing frequency Blood pressure returned to normal or high normal levels The vascular responses throughout this period showed wide variation with considerable lability of the pulse and blood pressure Often a slow pulse and low diastolic pressure appeared After a period of diminished urine output of varying duration and degree the patient had diuresis with subsequent disappearance of the uremic state

By the third or fourth week most of the symptoms and signs had disappeared or were greatly diminished and during the next few weeks weight strength and renal function returned to normal There usually was no residual damage or incapacitation

[This disease has been the subject of intensive study by a large group of experts The epidemiology and etiology still seem myst rious but with experience the cl nical management of individual cases has improved with gratifying reduction in fatality rate—Ed]

Clinical Observations in 100 Cases of Infectious Mononucleosis and Results of Treatment with Penicillin and Aureomycin are reported by Alvin L Schultz and Wendell H Hall[9] (V A Hosp Minneapolis) Diagnosis was based on clinical findings lymphocytosis over 50% and a heterophil antibody titer of 1 56 or higher All three criteria were fulfilled in 81 cases Diagnosis was made in the absence of a significant heterophil antibody titer in 16 cases but in all others classic findings of the disease were present Atypical lymphocytes as described by Downey were found in all cases Comparison of the occupations of the patients with those of 187 consecutive patients admitted for other diseases revealed significantly fewer laborers and farmers and more office workers students

(9) A I t M d 36 1498 1512 J 1952

and hospital employees among the infectious mononucleosis group

Both fever and lymphadenopathy were present in 93% of cases Early in the course the temperature curve was frequently spiking sometimes rising to 105 F Among the respiratory symptoms sore throat was the most common The posterior cervical lymph nodes were palpable in almost all patients Pharyngitis occurred in 68% and was often exudative or membranous with involvement of the tonsils Diagnosis was difficult from the history and results of physical examination alone only 48% of the cases were diagnosed correctly on admission Acute leukemia diphtheria brucellosis infectious hepatitis poliomyelitis duodenal ulcer and myocardial infarction were some of the erroneous diagnoses

Only 14 patients had normal leukocyte counts during their entire hospital stay most of them had leukocytosis Leukopenia when found occurred early and was followed by leukocytosis with a predominance of lymphocytes Only one patient consistently had less than 40% lymphocytes Nine patients had false positive serologic reactions for syphilis all reactions everted to negative within four weeks Results of the bromsulfalein and all the liver flocculation tests were normal in only 8% Five patients had pneumonitis demonstrable by a chest x ray

Penicillin was given to 36 patients and aureomycin to 15 26 received no antibiotics and served as controls Dosage of penicillin was 50 000 100 000 units intramuscularly every three to four hours Dosage of aureomycin was 0 5 Gm orally every six hours Duration of therapy varied from 7 to 10 days About 50% of the patients receiving penicillin or aureomycin showed clinical improvement evidenced by a great decrease in fever toxicity and sore throat within 48 hours after therapy was begun There was no significant difference in average duration of symptoms in the treated and control groups

Until recently it was felt that absence of anemia was an important point in differentiating this disease from acute lymphatic leukemia However in the past five years several instances of anemia associated with infectious mononucleosis have been reported In the present series there were three patients with a striking fall in hemoglobin level In two the anemia was probably hemolytic

Isolation of Virus as Cause of Behçet's Disease This disease first described by Behçet in 1937 has three cardinal symptoms (1) iridocyclitis with hypopyon (2) aphthae in the mucosa of the mouth and (3) ulceration of the sexual organs Both eyes are always affected sometimes simultaneously sometimes separately Typical aphthae can be observed in all parts of the mouth and on the tongue Lesions are found on the skin of the scrotum and on the large and small labia and clitoris Erythema nodosum may be associated with the disease as well as rheumatismal pain phlebitis anemia headache and signs of meningoencephalitis The disease recurs frequently and all three cardinal symptoms appear

F Necdet Sezer[1] reports on a study of over 30 patients with this disease at the University of Istanbul Attempts to produce an experimental disease in the eyes of rabbits with material from the anterior chamber or aphthae of these patients were unsuccessful Cultivation and serial passage of the virus obtained from three patients were performed For cultivation of the virus the vitreous taken from the enucleated eye of one patient and the subretinal serous fluid collected from two others were inoculated into the chorioallantoic membranes of fertile eggs The agent seemed to be transmitted subsequently to mice and rabbits by intracerebral inoculation

Results of complement fixation tests against the virus were positive with the serum of all patients with recently active disease and were negative with a limited number of normal control serums The virus caused typical encephalitis in mice produced in the eyes of rabbits an experimental disease similar to the disease in man and killed guinea pigs by causing hemorrhagic lobal pneumonia It passed through a Seitz filter with double pads According to the electron microscope photographs the diameter of viral particles is about 100 mμ

Results of this study seem to confirm the supposition that this syndrome with its three cardinal symptoms is an independent disease and to establish its causative agent as a filtrable neurotropic virus with specific characteristics first isolated in the course of these studies

[This report s ems impressive Confirmation should not be difficult. —Ed]

(1) Am J Ophth 36 301 314 M h 1953

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THE CHEST

CARL MUSCHENHEIM M D

PART II

THE CHEST

NORMAL AND PATHOLOGIC ANATOMY

Leonardo da Vinci and the Bronchial Circulation In reviewing the history of the bronchial circulation Leon Cudkowicz[1] (Post grad Med School London) points out that although a great deal had been written before the 19th century on the possible significance of the bronchial arteries no references appear in these texts to the observations on the bronchial circulation made by Leonardo da Vinci nearly 500 years ago A recent exhibition in London of the drawings of Leonardo included a reproduction of a drawing from the *Quaderni d anatomia* II Ir (Royal Windsor Library) in which the trachea and bronchial tree of the left lung with its accompanying bronchial arteries are depicted (Fig 7) The bronchial arteries are shown to arise from the aorta and to follow the individual bronchi to their termination In the same drawing (Fig 8) a circle is seen at the inferior margin of the lung which surrounds a terminal basal bronchus A line runs from this circle to the adjacent script which has been translated in the exhibition catalogue as

Nature prevents the rupture of the ramifications of the trachea by thickening the substance of this trachea and making thereof a crust like a nutshell and it is cartilaginous and in the interior remains dust and watery humour

This is said to be one of the earlier descriptions of a tuberculous cavity Closer scrutiny of the cavity reveals the remarkable feature of small bronchial arteries within its periphery It is impossible to say if Leonardo deliberately intended to show these systemic arteries reaching the walls of the cavity or if the vessels depicted were merely branches destined to follow the bronchus containing the peripheral cavity The latter explanation is probably the more likely

Microscopy of the vasculature in the vicinity of tubercu

(1) B t J T b rc 47 23 25 J ry 1953

Keele (1952) in a monograph on Leonardo s study of the heart and blood quotes from Leonardo s notebooks

Why nature duplicated artery and vein in such an instrument



F g 8—D t l f d w g by L d d V n f b on h l rte f ll w g l ft t l b h T t cul ty h w n t f l ft b l gm t A n d t l h l t ty f ty (F m C dk w L B t J T be c. 47 3 5 J y 1953 R p od d by pe m n f H M j ty Th Q)

one above the other finding them elves for the nourishment of one and the same member (the lung)

You may say that the trachea and the lung have to be nourished but if you had to do with a single large venarteria this could not accompany the trachea without great interference with the move



F g 10—L t al x f l ft l g w th t t m d m j t d nto b h l rt (A) d b h l t (B) (C t y f C dk w L. B t J T b 47 3 25 J u ry 1953)

tion of organs as much as the accuracy of his drawing emphasizes his exceptional skill as an academic anatomist Those who have tried to dissect the bronchial arteries even under most modern conditions know the hazards involved in tracing these delicate structures Without the use of contrast mediums

ment which the trachea makes in dilatation and contraction as well as in length and thickness Wherefore for this nature gave a vein *and artery to the trachea which would be sufficient for its life and* nourishment and somewhat removed the other large branches from the trachea to nourish the substance of the lung with greater con

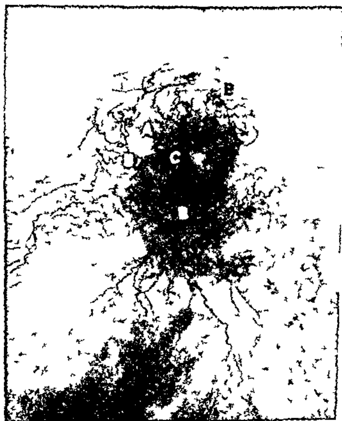


Fig 9—Lateral x r y of left upp l be sh w g *A* t berc lou cav ty *B* bro h al a t ri n on d rabl n nber in ts vi ty, *C* b on h al art y t minat i g in ts wall (Court y of Cudk cz L Lr t J T be c 47 3 25 January 1953)

venience (*By trachea Leonardo refers to the whole bronchial tree*)

This teleological view of the function of the bronchial circulation expressed about 300 years before Reisseisen and von Sömmering s definition of the bronchial arteries as the vasa nutritiva of the lungs is so modern in conception that little can be added It bears testimony to Leonardo s grasp of func

[Studies in pulmonary physiology have thrown much light on the functional impairment in pulmonary emphysema but little is known concerning the pathogenesis of the various types of this crippling disorder These observations on the pathology of the bronchial arteries appear to point the way to finding some of the causes —Ed]

Observations on Anatomy of Intrasegmental Bronchial Tree are presented by John Hayward and Lynne McA Reid[3] (Royal Melbourne Hosp) The posterior basal segment was most exhaustively studied and enough examples of other segments were examined to show that the general pattern of bronchial arborization is the same in all The bronchi of fixed specimens were exposed by cutting with scissors along their length Side branches thus exposed could then be followed Portions of each air tube between successive subdivisions were called generations and these were counted up to but not including the respiratory bronchioles

In each bronchopulmonary segment there are several axial pathways As these continue to the surface most peripheral from the hilus they continue so far into the segment still with a considerable diameter that they possess an individuality not shared by the lateral pathways In the multitude of bronchial divisions they can be clearly distinguished in both specimens and bronchograms and they appear as a framework for the lung tissue which fills the space between and around them The side or lateral branches from axial pathways run a shorter course and soon divide into finer branches which fan out widely to supply the more proximal lung tissue in the segment (Fig 11) The segmental bronchus enters the top left hand corner Four or five axial bronchi are present and the longest passes to the portion of the segment which fills the posterior costophrenic angle Passing outward from the segmental bronchus at some points of division both of the branches continue as axial pathways and at others one is clearly a side branch which continues as a lateral pathway while the other proceeds axially

The maximal number of generations for the posterior basal segment was between 20 and 25 from the segmental bronchus to the most distal terminal bronchiole usually to the lung tissue in the costophrenic angle In other segments there were slight variations which seemed to be related to their length For instance the lingula gave similar maximal figures

(3) Th 7 89-97 Ma h 195

and careful microscopy modern studies of this circulation would be almost inconceivable (Fig 10)

Leonardo da Vinci s mirror writing his use of the vulgar tongue the intellectual indifference of his contemporaries and the long incarceration in past centuries of his notebooks in private hands may perhaps have been responsible for medicine s disregard of these remarkable observations

Bronchial Arteries in Pulmonary Emphysema L Cudkowicz and J B Armstrong (Post Grad Med School London) made histologic and roentgenographic (with radiopaque injections via the aorta) postmortem studies of the bronchial arteries in 18 cases of chronic bronchitis and emphysema Four distinct types of pulmonary changes were observed

Obliteration of intrapulmonary bronchial arteries and dense pleural adhesion formation were found in the senile type of atrophic emphysema visceral pleura elastic structures in the periphery and the smaller bronchi seemed to have lost their arterial blood supply In a younger group of patients with clinical pulmonary insufficiency and without bullous emphysema there were no pleural adhesions and bronchial circulation was almost totally occluded

An intermediate group of patients showed obliteration of the intrapulmonary bronchial arteries pleural adhesions and in addition anastomoses between the bronchial and pulmonary arteries in one lobe only

In a final group in which the hemodynamic changes of cor pulmonale were pronounced there were profuse anastomoses between the vasa vasorum of the pulmonary arteries (which are derived from the bronchial arteries) and the pulmonary arteries themselves This was associated with obliteration of the normal peripheral bronchial artery bed and changes in the wall of the larger pulmonary artery trunks The bronchi and lung tissues showed severe atrophy and fibrosis while part of the pulmonary artery bed served merely as a route for arterial blood to reach the proliferating collagen in the atrophic lung areas

Changes of this type probably throw a burden on both ventricles and the expectation of life may become reduced as a result of peripheral anoxia as a whole and the ischemia of the lungs and heart in particular

(2) Thorax 8 46 58 Mar 1953

fairly regular intervals of only a few millimeters until the pathway ends with a small cluster of terminal bronchioles which are even closer together (Fig 12) The bronchial part occupies two thirds to three quarters of the length of the pathway Lateral pathways are shorter and contain fewer divisions but the relative spacing of the branches in each part is the same as in axial pathways

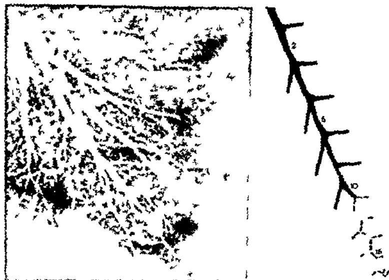
In the bronchial part of the tree two sorts of division are seen The more frequent is characterized by an acute angle and a well defined carina between the branches Often both branches of such an acute angle division may lead to bronchial pathways of equal lengths and although sometimes one is the beginning of a shorter lateral pathway this can be ascertained only by following both to the periphery In the second type the wide angle division the parent stem can be clearly distinguished from the side branch In the bronchiolar part the angle between divisions is always fairly wide there is no true carina and the branches appear as a hole in the side wall of the bronchiole Each of the side branches of an axial bronchiolar pathway ends at once or after only a few further divisions in a similar cluster of terminal bronchioles Bronchioles are frequently visible in normal bronchograms but it is scarcely ever possible to trace a bronchiolar pathway in its entirety In films most suitable for clinical purposes with the bronchi clearly shown bronchiolar filling is incomplete and when the bronchioles are well filled overlying shadows of lipiodol* in other tubes and in the alveoli obscure them

The bronchi taper from hilus to periphery and in general their progressive narrowing is greatest near the hilus and becomes less rapid as they become smaller The narrowing occurs mainly at points of division rather than gradually all along the length Portions of bronchi between divisions are almost exactly cylindric The bronchioles are all of approximately the same diameter which is of the order of a few millimeters They taper only slightly toward the periphery

This method of localizing areas in the lung by generation is useful in both anatomy and pathology Recording the diameter of the air tube in describing the presence of mucous glands or cartilage as is done by anatomists is unsatisfactory because of variation in sizes of persons variable shrinkage and alteration by disease It is more accurate to state that cartilage

but in the apical segment of the lower lobe which is shorter the average figure was nearer 20 The variation in counts in corresponding segments of different adult lungs did not amount to more than several generations Figure 12 is a diagrammatic representation of the divisions along an axial pathway in a posterior basal segment

The bronchial tree divides itself into proximal and distal



F g 11 (l ft) —N mal post o b n h pulm n y s gment
F g 12 (ght) —D ag am of b n h f a l p thw y Th segm tal b onch s c n de ed the fi st g n at n th b n h f m t fi st d v s on th se o d g ne s and on Th p ox m l 10 g n at ns d wn n a on tin ou bl k l ne to nd at x t l g in th w lls P phe al g erat s (n cartil ge) a draw n d tted l n
(Courte y of Ha wa d J nd Re d L McA Thor x 7 89 97 M h 1952)

parts distinguished by the different shape and mode of branching of the tubes This variation corresponds to the division into bronchial and bronchiolar parts made on the basis of the presence of cartilage *The branches of the bronchial tree arise about three times closer to each other at the periphery than near the hilus* If an axial pathway is followed the average interval between branches for the first 8 or 10 generations (which comprise the bronchial part) is about 1 cm Over this length the points of division are usually irregularly spaced In the bronchiolar part the subdivisions occur at

events depend on many factors the most important of which is the fate of the contents of the necrotic node Lymph contents that are liquefied at time of perforation may be completely emptied and the node collapses and quickly heals With a



F g 13—Lymph l p f t w th lt g q t l p t filt t L g pe m f m g l ½ wh d d f t b l m g t ft l h p m y f ct F p y f u pe ppe bo d t m ddl l be I p tly e t t d lymph d h g p t filt t l w egm t f m d ll l b F be l p t b h p t d f d ff lymph d o- b hog t b cul p t t Tw m ll pe f d f ct lso pr t th P b p t t p f t d f t f th m d ll lobe b h ft d h g f f t l ou lymph od f th p l t l t lob p (C y f S hw t P Am R T l 67 443 452 Ap l 1953)

large enough perforation and no liquefaction the entire node made be extruded as a sequestrum Such a node may also organize and calcify and the perforation defect become scarred With partial liquefaction a bronchial fistula which may heal as the node organizes (Figs 13 and 14) results Both penetration and perforation result from progression of the infection

disappears from the walls of air passages at about the 10th generation in axial pathways Pathologists simply regard everything subpleural in position as peripheral in origin an assumption not always justified Only three to five generations occur between the segmental bronchi and the saccules of saccular bronchiectasis thus proving that the saccules arise from lesions extending well into the proximal part of the bronchial tree and that their subpleural position is due to destruction of the bronchial tree and lung tissue distal to this level In massive collapse only about five proximal generations of segmental bronchi remain patent In cylindric bronchiectasis about eight bronchial generations fill with lipiodol * In some cases it is useful merely to indicate which part of the bronchial tree is involved without bothering about actual counts For example in bronchiectasis the dilated tubes are nearly always confined to the bronchial part of the tree and in bronchopneumonia the main lesions are in the bronchiolar part

[This careful study indicates that not all pulmonary lesions which appear to be peripheral are so in a true anatomic sense The applications relate not only to a better understanding of th pathology of bronchiectasis bronchopneumonia and massive collapse but also to such isolated lesions as pulmonary cysts tuberculomas and peripheral tumors —Ed]

Role of Lymphatics in Development of Bronchogenic Tuberculosis *is discussed by Philip Schwartz*[4] *(Univ of Istanbul) on the basis of 700 cases*

Tuberculous nodes involve the airways by extrinsic compression usually the mechanical result of grossly enlarged nodes Penetration of the bronchus by tuberculous infiltration of the bronchial wall extending from the lymph node along the lymph channels which connect the peribronchial tissues to the mucosal epithelium may occur before necrosis of the entire node and before destruction of the node capsule Small erosions representing open foci and sources of reinfection between the cartilage bars are often the first sign of lymph node penetration Several neighboring foci may fuse producing extensive protrusion of granulation tissue which replaces the bronchial mucosa and may cause narrowing even of the larger bronchi

Necrosis and rupture of the area of bronchial infiltration transforms the penetration into a perforation Subsequent

(4) Am R T be c 67 440 452 Ap 1 1953

Lymph node perforation usually causes inflammatory con solidation in the parenchymal sector supplied by the involved bronchus Involvement of large bronchi may also affect sev eral neighboring lung segments but perforation and emptying of a tuberculous lymph node into the bronchial system do not



F g 15 —Old p f t A l g t l k s n a l ft pp l be b h th lt f ld p f t wh h d th ld d p hymal l N th p l t (C t y f S hw rt P Am R T be 67 440 452 Ap l 1953)

always result in lung involvement Many cases with large lymph node perforations showed only minimal or no disease of the lung In others extensive parenchymal lesions were asso ciated with apparently insignificant bronchial lesions De velopment of infiltration from lymph node perforations depends not only on the quantity of infectious and toxic mate rial discharged into the bronchi but also on the sensitivity

Failing Lung According to William S McCann Frank W Lovejoy Jr and Paul N G Yu (Rochester N Y) the concept of the failing lung in contrast to the failing heart has been slow to enter the thinking of clinicians Although the interrelationships of the functions of ventilation and circulation are intimate situations in which the ventilatory mechanism is primarily at fault must still be differentiated from those in which the primary deficiency is circulatory Circulation may fail from extracardiac causes as in shock and ventilation may fail from extrapulmonary disorders such as morphine narcosis Among the acute pulmonary diseases which lead to primary lung failure are the bronchopneumonias with their characteristic combination of atelectasis and emphysema which may threaten suffocation by impairment of ventilation of the alveoli In lobar pneumonias when only one or two lobes are involved the blood supply of involved lobes is diminished and that of uninvolved lobes is increased together with increased ventilation of those lobes The carbon dioxide tension of the blood tends to decrease The hypocapnia of lobar pneumonia is associated with rapid shallow breathing and a tendency to peripheral circulatory collapse Bronchopneumonias in sharp contrast are more apt to be associated with increase in the carbon dioxide tension or hypercapnia and have a greater tendency to bring on congestive failure

The chronic lesions of the lung which may lead to its failure are characterized by some form of obstructive emphysema and a tendency to vascular sclerosis in the lesser circulation To these may be added chronic atelectasis and replacement fibrosis thickening of the alveolar wall as in beryllium granulomatosis chronic bronchial disease with or without bronchiectasis and adhesive pleuritis Whatever the primary cause the chief determining factor in the genesis of failure of the lung is the degree of emphysema Its physical signs are so unobtrusive its appearance in chest x rays so inconspicuous or so easily obscured by more spectacular lesions that physicians tend to forget it until some intervening condition precipitates pulmonary failure Emphysema can easily be measured by de

(5) N w Y k J M d 52 1983 1986 A g 15 195

of the lung tissue and the constitutional resistance of the patient

Systematic search for lymph node perforations into airways revealed fresh defects or scar in approximately 25% of patients who came to autopsy and in 90% of those with active pulmonary tuberculosis Tuberculosis therefore appears to be a *lymph node disease* infiltrations and the destructive process seen in the lung are usually secondary to perforation of the bronchi by tuberculous lymph nodes This is true even of the parenchymal disease associated with the first exogenous infections When the exact time of such infection could be established *lymph node perforation into the bronchial system* often appeared within four to six weeks of penetration by tubercle bacilli Although pulmonary foci resulting from exogenous infection generally remain clinically undetectable *the lesion resulting from lymph node perforation represents* the beginning of the lung disease proper Depending on the immunologic state of the patient the resulting parenchymal disease may disappear almost completely or progress to extensive destruction

If the patient survives the initial insult the infiltration may disappear and large foci of destruction may become encapsulated The bronchial perforation may heal with a scar *apparently stopping the entire process The infected person* may never show signs of active pulmonary tuberculosis Virulent tubercle bacilli may remain viable for years mainly in intrathoracic lymph nodes and grow again under opportune conditions *If the disease is reactivated the decisive* events take place in the lymph nodes Revitalized tuberculous infection in the nodes penetrates into the bronchial wall and new lymph node perforations appear creating new areas of *parenchymal infiltration A tuberculous process* beginning in childhood may cause recurrent exacerbations for decades through recurrent exacerbations within lymph nodes and result in bronchial perforations and new areas of pulmonary disease

[Lymph node perforations into the bronchial system giving rise to progressive parenchymal lesions *have hitherto been regarded as relatively* infrequent and especially so in the adult or reinfection form of pulmonary tuberculosis This concept of the pathogenesis of chronic phthisis challenges the long accepted principle that lymph node involvement is neither conspicuous nor important in the majority The evidence here presented is impressive with respect to both the significance and the frequency of the phenomenon —Ed]

in such instances may be lethal and further depression of ventilation by narcotics of the opium group should be carefully avoided

When emphysematous patients with chronic pulmonary disease are under observation the following may herald pulmonary or ventilatory insufficiency (1) increasing elevation of the CO combining power of the blood and progressive increase in the arterial carbon dioxide tension (2) failure of carbon dioxide added to the inspired air to produce a normal increase in pulmonary ventilation (3) progress of mental confusion to stupor or coma while cyanosis is relieved by administration of oxygen (4) acceleration of circulation time before signs of congestive failure appear or normal circulation time in patients with congestive failure

The term pulmonary insufficiency or ventilatory insufficiency is preferable to cor pulmonale or pulmonary heart disease If circulatory failure is mistaken for ventilatory failure valuable time may be lost and harm may be done by use of digitalis morphine and oxygen when the patient most urgently needs artificial increase in ventilation aided by aminophylline or bronchodilator drugs

[This brief description of pulmonary failure merits careful reading in the original It will be appreciated for the clarity of presentation of the essential concepts of pulmonary insufficiency as well as for the practical suggestions concerning therapeutic management—Ed]

Precipitation by Pulmonary Infection of Acute Anoxia, Cardiac Failure and Respiratory Acidosis in Chronic Pulmonary Disease Pathogenesis and Treatment. Daniel J Stone Arthur Schwartz Walter Newman James A Feltman and Francis J Lovelock[6] (V A Hosp Bronx N Y) discuss experience with four patients with chronic pulmonary disease and variable degrees of pulmonary insufficiency Functional studies made after recovery in three revealed a clearcut emphysema pattern Clinical examination shows inadequate bellows motion of the chest and bronchial obstruction secondary to chronic bronchial infection These plus difficulty in proper distribution of gases result in alveolar respiratory insufficiency leading to a chronic state of ineffective alveolar ventilation characterized by arterial anoxia and hypercapnia and possibly decrease of arterial pH Such patients are susceptible to repeated bouts of acute bronchitis and bronchopneumonia which

(6) Am. J Med. 14 14 2 J ry 1953

termining the total lung volume and relating the diminished vital capacity to the increased residual air or other alterations in the fractions of the pulmonary capacity Generally as these relationships become more and more abnormal arterial blood saturation tends to decrease and carbon dioxide tension to increase In the compensation for the gradual retention of carbon dioxide there is usually some increase in the alkaline reserve of the blood and not infrequently some increase in the number of red cells with microcytosis In such patients the respiratory center is less than normally sensitive to carbon dioxide and the response in ventilation to addition of carbon dioxide to inspired air will be diminished

This gradual process by which hypercapnia and its compensation develops may go on so slowly that neither patient nor doctor are concerned over it until pulmonary failure develops One of the commonest of the precipitating events is acute bronchitis With fever and cough cyanosis may become alarming and orthopnea with asthmatic breathing may be noted not infrequently with evidence of increased venous pressure and even edema The patient becomes somewhat stuporous and confused Respirations may become slow and shallow If oxygen is given by mask or nasal catheter the *patient may lapse into coma even though cyanosis may be* relieved The optic disks may be choked If oxygen administration is discontinued partial consciousness may return with cyanosis In the authors experience and that of others correct management involves resuscitation by artificial respiration in an iron lung By increasing the ventilation hypercapnia is relieved acidosis corrected and sensitivity of the respiratory center restored so that it again responds to its normal stimuli Administration of oxygen should be undertaken gradually after there is evidence of improved irritability of the respiratory center Once compensation has been re established patients have maintained it for some time When confronted with a cyanotic patient in an emergency such that the facts concerning the tension and content of carbon dioxide in the blood are unknown the effects of relieving cyanosis by oxygen administration should be followed If cyanosis is eliminated but the patient lapses into a deeper coma primary failure of the ventilatory mechanism rather than a primary failure of the circulation is present Continued use of oxygen

the aerosol epinephrines are helpful In view of the cyanosis oxygen therapy is necessary and should be instituted immediately but with extreme care taken to observe the patient s ventilation and mental responses When possible arterial gas studies should be performed if not serial observation of CO_2 combining power should be made a rise indicating probable increasing respiratory acidosis If increasing mental stupor or confusion decrease in ventilation a significant increase in the arterial pCO_2 or decrease in pH is noted durin oxygen therapy artificial respiration is indicated immediately In addition to increasing effective alveolar ventilation the respirator is also valuable in mechanical removal of bronchial secretions If a respirator is readily available it should probably be used at onset of therapy instead of waiting for unfavorable signs to be produced by oxygen alone The Drinker Collins type of respirator is satisfactory The patient tends to be relaxed in it and it permits frequent aspiration of pharyngeal secretion without interference with oxygen administration by nasal catheter With this management rapid response of cardiac failure has been noted without use of digitalis although it should be used when indicated

Cardiopulmonary Function in Pulmonary Form of Boeck s Sarcoid and Its Modification by Cortisone Therapy According to John H McClement Attilio D Renzetti Aaron Himmelstein and Andre Cournand[7] (Columbia Univ) conflicting results of physiologic studies in pulmonary sarcoidosis may be due to different types of abnormalities found in this condition In 10 cases three distinct types were observed (Tables 1-4)

Cases 1 4 represent the first type characterized physiologically by (1) reduction of all lung volumes usually with a normal ratio of residual volume to total capacity (2) normal index of intrapulmonary mixing (3) normal or slightly reduced maximal breathing capacity (4) mild hyperventilation at rest and during recovery from exercise (5) normal arterial O_2 saturation at rest and normal or slightly reduced values after exercise (6) normal O_2-diffusing capacity (7) normal or minor abnormalities of ventilation perfusion characteristics and (8) mild pulmonary arterial hypertension

Cases 5 9 represent the second type characterized by (1)

(7) Am. R T b 67 154 17 F bru y 1953

usually respond to penicillin or other antibiotics Occasionally bronchial obstruction due to infection is so severe that effective alveolar ventilation is further diminished leading to acute anoxia and carbon dioxide retention Diagnosis of infection was especially difficult because only one patient was febrile and only one had leukocytosis Anoxia and profound cyanosis had developed and definite signs and symptoms of cardiac failure were noted This constituted the first cardiac episode in these patients

Such patients undoubtedly have chronic pulmonary artery hypertension manifested by large pulmonary arteries on x rays loud second pulmonic sounds and ECG evidence of right ventricular hypertrophy Anoxia has been implicated as one mechanism responsible for pulmonary artery hypertension Acute right heart failure in these four cases can be reasonably explained by just such a mechanism In each patient arterial gas studies during the acute infection revealed profound anoxia In one signs of congestive heart failure completely disappeared in 24 hours without specific therapy directed toward it This can be attributed to relief of anoxia by oxygen therapy artificial respiration bronchodilators and antibiotics

The final sequence in development of this clinical picture occurs with the placing of the patient in an environment of high oxygen concentration Respiratory acidosis due to further retention of carbon dioxide occurs due undoubtedly to removal by relief of anoxia of the stimulus to ventilation operating through the carotid receptor mechanism Rapid onset of stupor and even coma on exposure to oxygen sometimes of only two hours was striking Conversely on withdrawal from high oxygen concentrations mental disturbance rapidly clears In all cases the onset of symptoms could be correlated with hypercapnia and acidosis which is responsible for the abnormal mental state is not known

Therapy based on physiologic considerations should include establishment of an adequate airway and improvement of effective alveolar ventilation Infection with excessive secretion and possible accompanying bronchial spasm is the major factor in diminishing the airway Control of the infection with adequate antibiotic therapy particularly penicillin is of primary importance at onset Bronchodilators such as

treated patients with this pattern showed no definite evidence of physiologic improvement

Only Case 10 represents the third type in which lung volume changes and disturbances in gas exchange are those of severe chronic pulmonary emphysema Cortisone caused a satisfactory clinical response striking roentgen clearing of pulmonary infiltrations and improvement in O_2 transport to the pulmonary capillaries This improvement resulted from a de

TABLE 2 —VENTILATION AND RESPIRATORY GAS IN ARTERIAL BLOOD

CA	DD	NTILATIO l/ n./m		LOO		
				TU ION		pCO
		Res	E rc se	Res	Recov ry	
				per en	per t	mm. Hg
Norm l		3 4	10 6	93	93	33
1 R S		5 5	10 5	94	94	34
2 T P		4 8	14 5	95	93	37
3 J B		4 0	9 6	96	90	43
4 A B		5 0	15 8	96	98	34
5 R B		6 6	10 1	94	—	35
6 C L	B f th py	6 6	14 4	94	81	40
	Aft 4 w k of th apy	5 7	—	99	95	33
7 W A	Bef th apy	5 3	12 0	95	89	33
	Aft 3 d y f th py	4 6	—	98	96	36
	Afte 4 week f th py	4 5	7 9	96	93	35
8 L W	B f th py	7 1	14 7	96	74	40
	Aft 9 w k f th py	6 3	16 7	94	75	33
9 Q G	B f th py	5 4	11 4	9	61	9
	Afte 3 w k f th py	6 2	15 9	88	57	40
10 P B	B f e th py	8 8	—	85	—	42
	Aft 4 w k f th py	7 4	—	97	—	36
	9 m th l t	7 4	—	87	74	35
	Afte 3 w k f th py	8 8	15 8	93	6	37

crease in venous admixture in the arterial blood without significant change in the O diffusing capacity Furthermore the lung volume changes consistent with chronic pulmonary emphysema persisted It is apparent that the emphysematous lesions in this case were not reversible by hormonal therapy and played a significant part in the physiologic disturbances

Lacking biopsy studies of the lung before and after cortisone therapy it is difficult to decide why no uniform response was observed From extrapulmonary biopsy studies it appears that granulomatous lesions tend to become fibrotic under treatment It is likely that a similar process takes place in the lungs Therefore it might be assumed that changes in pulmonary

reduction of the lung volume with normal ratio of residual volume to total capacity (2) normal index of intrapulmonary mixing (3) well maintained maximal breathing capacity (4) marked hyperventilation at rest and during exercise (5) normal or slightly reduced arterial O saturation at rest and considerable unsaturation on exercise (6) reduced O_2 diffusing capacity (7) variable disturbances in ventilation per

TABLE 1—LUNG VOLUMES INDEX OF INTRAPULMONARY MIXING AND MAXIMAL BREATHING CAPACITY IN PULMONARY SARCOIDOSIS

Case	Time of study	Vital capacity per cent predicted	Residual volume per cent predicted	Total lung capacity per cent predicted	Residual volume / total capacity × 100	Maximum breathing capacity per cent predicted	Index of intrapulmonary mixing
Norm l		100	100	100	<35	100	<2 5
1 R S		43	64	50	[illegible]5	90	1 4
2 T P		59	96	64	27	69	1 9
3 J B		81	56	77	15	95	1 5
4 H B		76	68	81	16	103	0 8
5 R B		43	66	50	35	93	1 6
6 C L	Befo e therapy	43	60	46	26	[illegible]5	1 0
	After 4 weeks f therapy	61	52	60	17	[illegible]9	1 0
7 W H	B fore th rapy	68	104	78	27	77	0 9
	After 4 weeks of the py	9	63	6	17	101	1 5
8 L W	Before therapy	32	63	38	44	67	1 0
	After 9 weeks of the py	61	42	56	19	89	0 5
9 Q G	B fo e the py	49	8	56	36	100	1 3
	Afte 3 weeks of th py	57	90	66	35	107	1 1
10 P B	Bef th py	55	2"8	112	64	[illegible]4	3 4
	Afte 4 w ks f th r py	6	177	95	48	[illegible]6	1 4
	N ne mo th lat	52	169	84	48	43	2 0
	Afte 3 w eks f th apy	58	183	90	53	[illegible]6	2 0

Poor co-op at on w s obta ned n d termin ng v tal ap ty

fusion relationships and (8) pulmonary arterial hypertension Of four patients given cortisone two had definite improvement in pulmonary function manifested chiefly by return of O_2 diffusing capacity to normal increase in vital and maximal breathing capacities and decreases in residual volume and degree of hyperventilation *In two patients after treatment* with cortisone the pulmonary arterial pressure was nearly normal at rest and during moderate exercise the other two

TABLE 4.—Hemodynamic Measurements

		PULS	P-	ST L- ENOU	SD IN	PUL TE		TE	
						/d†	m‡	/d	m
			cc /m	cc/l	l/m /	m Hg	mm Hg	mm.Hg	m Hg
N m t	R t	—	1 6	9	3 3	20 9	13	112/65	84
1 R S		97	14	38	3 7	3 /11	24	141/88	110
		(1 0)	(314)	(65)	(4 8)	(41/16)	(29)	(161/95)	(123)
3 J B		86	—	—	—	2, /12	17	150/97	1 3
		(100)	(?90)	(56)	(5 2)	(3 /14)	(21)	(16 /101)	(1)
5 R B		111	—	—	—	27/10	16	—	—
6 C L	B f	104	168	53	3 2	3 /13	21	13 77	98
	th py	(103)	(0)	(60)	(3 7)	(41/15)	(28)	(143/79)	(97)
	Aft 4 w k f th py	63	133	44	3 0	27/15	19	141/8	104
7 W H	Aft 3 d y	3	169	35	4 8	16/8	1	1?? 80	98
	f th py	(120)	(16)	(63)	(8)	(4/17)	(20)	(131/84)	(104)
8 L W	B f th py	110	16	41	3 6	34/15	24	—	—
	Aft 9 k f th p	8	1 1	46	7	3 /17	6	115/84	99
9 Q G	B f th py	100	146	43	3 4	58/ 5	30	11 /66	85
	Aft 3 w k f th py	100	158	38	4 2	51/16	34	109/68	85
10 P B	B f th p	100	187	60	3 1	54/ 4	35	95/71	84
	Aft 4 w k f th py	85	156	51	3 1	50/27	37	170/105	131
	9 m th l t	95	143	46	3 1	45/21	32	9 /68	78

( ) F g n p th p t d t I t d d g t dy t t

M m nt f ca d tp t t t t h lly t f t y
† /d = y t l /d t l
‡m = m

degree of ventilatory insufficiency treatment seems unwarranted at present and (2) to provide objective measurements of the effect of treatment

PHYSICAL DIAGNOSIS AND DIAGNOSTIC PROCEDURES

So called Middle Lobe Syndrome Chronic atelectasis and pneumonia of the middle lobe have been described as a clinical syndrome of which the essential pathologic feature is obstruction of the middle lobe bronchus Bjarne Fretheim[8] (Univ

(8) Th 7 156 158 1952

function on hormonal therapy are related to the degree of resolution of the granuloma and extent of resulting fibrosis Thus failure of improvement in pulmonary function might be due to development of severe fibrosis or to the fibrotic nature of lesions before treatment These same considerations might

TAPLE 3—MEASUREMENT OF VENTILATION PERFUSION RELATIONSHIP AND O DIFFUSING CAPACITY

	ME STU	DEAD AC LA ON DN NT TOT LA	L LA pO_2 ROO	A 2 AD NT LS Room A	Low O	PUS O CA ACITY (DLO₂)	AD IXTO PE NT AC OUTPUT
			mm Hg	mm H	mm Hg		
Norm l		<30	100	12	12	15	<6
1 R S		23	114	18	4	>14	<10
2 T P		3?	104	19	6	—	—
3 J B		4	103	14	5	>23	8
4 H B		?0	116	29	7	—	—
5 R B		36	108	26	23	7	12
6 C L	B f e the py	40	110	35	28	8	16
	Afte 4 we ks of th apy	32	113	10	3	18	3
7 W H	B fo e the py	4	104	20	23	—	—
	Afte 3 d ys f th apy	22	108	16	3	3	8
	Afte 4 w k of th py	16	110	19	7	—	—
8 L W	B f e th apy	44	111	34	?9	7	13
	Aft 9 week f th rapy	3?	114	29	27	5	9
9 Q G	B f r th apy	39	107	51	49	4	20
	Aft 3 we k of the apy	40	106	35	30	5	13
10 P B	Befo th apy	58	103	40	37†	6	12
	Aft 4 ek f th r p	42	112	28	30	5	6
	\ m the lat	47	106	51	46	5	?2
	Aft 3 w ks f th p	46	112	30	40	—	2

16* yg n †17 4* yg n

explain the variable and usually insignificant influence of cortisone on the hemodynamic findings

Apparently physiologic studies are not particularly helpful in the selection of patients who will benefit from hormonal therapy Their two greatest values may be (1) to confirm clinical impressions of severity of the disease and to demonstrate disturbances in pulmonary gas exchange which is important since in the mild form characterized only by a mild

these effusions the fluid was under positive pressure through all phases of the respiratory cycle It is not the height of pressure that is important but only the fact that it is elevated or positive The pressure must be sufficient to compress parenchymal tissue down to bronchi of sufficient size to produce these auscultatory findings The sustained positive pressures were found in patients with cardiac decompensations or carcinoma which tend to produce effusions with fairly rapid onset and containing much fluid An effusion due to an inflammatory process however could probably achieve the same results if acute and massive enough The other six patients had usual physical findings and showed negative pressure in the inspiratory phase

Effusions that had unusual findings but did not appear to be massive on x rays or percussion contained more fluid than effusions of equal height with the usual findings A thick effusion will be more likely to cause compression and yield bronchophony and tubular breathing than will an equally high but thin effusion

[These findings as the authors indicate are unusual only to the extent that they are atypical and not well known a circumstance which accounts for the frequent misdiagnosis of simple effusion as pneumonia —Ed]

New Medium for Bronchography After preliminary experimentation Conway Don[1] (Univ College Hosp London) found that dionosil a 50% aqueous suspension of a medium not soluble in water required special technic because its instillation produced severe coughing They worked out the following method

METHOD —With the patient hospitalized the procedure is carried out under a penicillin cover to reduce the risk of infection with cricothyroid puncture and of pulmonary complications Premedication consists of omnopon gr 1/3 scopolamine gr 1/150 and seconal® gr 1½ Preliminary rehearsal of posturing insures the patient's co operation The skin and subcutaneous tissues are infiltrated with 1 cc of 2% xylocaine® and 2 cc. is injected into the trachea as the patient inspires after holding the breath in expiration. With the bronchogram needle inserted and tied into the trachea 4 cc anesthetic is injected into each lung and spread by posturing The medium is then run in slowly in bilateral bronchography the right side is routinely filled first regardless of the side involved and about 16 cc is required for each lung Posturing is done by means of the tilting couch Peripheral filling is produced by two or three deep breaths when the posterior basal segments are filling two or three

(1) B t J R d l 25 573 578 N embe 1952

of Oslo) found that in 19 of 40 cases of post tuberculous or nonspecific bronchial stenosis the middle lobe was affected Frequent colds chronic cough and hemoptysis were the essential clinical manifestations In two cases the lesion was detected incidentally in apparently healthy persons The bronchoscopic findings were of little significance The radiologic picture consisted of atelectasis and fibrosis of the middle lobe in 10 cases bronchiectasis and stenosis of the middle lobe bronchus were found and in 7 there was a calcified lymph node adjacent to the middle lobe bronchus Ten patients were treated conservatively and 9 underwent surgery partly because a malignant lesion could not be entirely excluded

The term middle lobe syndrome although lacking an etiologic clinical or pathologic basis is of practical value as these changes are far more frequent in the middle lobe Differentiation between post tuberculous and nonspecific stenosis serves no purpose The essential problem concerns bronchogenic carcinoma The radiologic findings and results of bronchoscopy including biopsy and cytologic examination will be of determinant importance In this series there was one case in which the probable diagnosis was carcinoma but operation revealed nonspecific bronchostenosis On the other hand negative findings do not exclude carcinoma According to Brock carcinoma of the middle lobe is rare In 1 200 cases of bronchogenic carcinoma he found only 8 of tumor arising in the middle lobe Fretheim however among 125 cases of bronchogenic carcinoma found 11 with evidence of middle lobe tumor This is such a high incidence that the possibility of carcinoma must always be considered

Unusual Physical Findings in Pleural Effusion Intrathoracic Manometric Studies That increased breath sounds to the point of bronchial breathing and increased voice sounds can be associated with pleural effusions is not well known Modern texts make only passing reference to these unusual phenomena the emphasis being placed on the more typical signs

Arthur Bernstein and Fred Z White[9] (Univ of Illinois) found in 8 of 14 patients with pleural effusion pulmonary compression with dulness bronchophony or whispered pectoriloquy or both Manometric studies demonstrated that in

(9) Ann. I t Med 37 733 738 Octobe 1952

medium normally cleared away completely in three to four days A mild and transitory fever in seven patients and one somewhat more prolonged in five others were the only reactions

Dionosil s advantages over iodized oil include (1) complete clearing away within four days (2) since it is not oily operation need not be postponed after bronchography (3) its lower viscosity makes injection easier and permits use of a finer intratracheal needle (4) since alveolar filling is not normally produced by quiet respiration the procedure (unlike that with iodized oil) need not be hurried screening can be done at leisure unsatisfactory films repeated or inadequate filling repaired without obscuring the lung picture (5) since the bronchi tend to be outlined rather than filled detail is improved and (6) the medium can be used in active tuberculosis because inorganic iodine is not liberated Among its disadvantages are that it often causes pyrexial reactions involves a more elaborate technic requires hospitalization and is less radiopaque than oil

Clinical Experience with Water Soluble Bronchography Compounds Mordant E Peck Adrian J Neerken and Emmanuel Salzman[2] (Univ of Colorado) found on reviewing 56 consecutive bronchograms performed with methocel diodrast® that 33% had been unsatisfactory This compares with results obtained by others throughout the country who have used water soluble mediums Oily mediums have been found to give consistently better results of 528 bronchograms with lipiodol® only 15 9% were considered unsa isfa o y

Various difficulties are inherent in the use of water oluble mediums (1) The absorption of the contrast material (in all instances iodopyracet) is extremely rapid Hence to obtain results which are at all satisfactory it is necessary to become familiar with the u e of these mediums (2) The material miscible with the bronchial s cretions tends to fill the peripheral bronchial tree confluently in contrast to the picture obtained with iodized oils in which the bronchial tree is outlined and clubbing due to b o kage by retained secretions is observed These bronchograms must therefore be read from a somewhat different point of view than those with the iodized oil (3) Perhaps most significant is the fact that these

(2) J Th ra S g 25 234 45 M rch 1953

more when the anterior basal and middle lobe segments are filling and three or four as the upper lobe is filling

The result is examined fluoroscopically Further filling if required is simple and its adequacy may be confirmed by further screening The method conclusively demonstrates true bronchial blockage Without moving the patient from the couch antero posterior and right lateral films are taken for the right side and



Fg 16—B l t l b h g m bow g m l ght d l b h t f th p l a t d p t gm t f the upp l t th l ft d Not opaqu m d m n th ph g (C t y f D C B t J R d l 5 573 578 N embe 195)

anteroposterior and left posterior oblique films for the left On his return to the ward the patient is given frappage and postural drainage to clear the bronchi

The method has been used in 40 adults always with good results Despite the medium's lower radiopacity (the iodine content is 30% as against 40% in iodized oil) the bronchi were clearly visualized (*Fig 16*) *the more so as the medium* coated the bronchial wall rather than filling the bronchi The

symptoms Physical incapacity due to any cause except aging was absent in 75% Complications usually expected in association with bronchiectasis were relatively rare Only 9 patients had had pneumonia (only 2 twice) 17 of the 39 survivors with adequate histories had frequent and prolonged colds Only eight gave histories of hemoptysis during the follow up period and in none of these was bleeding copious Only seven survivors raised foul sputum and they did so only at the acute onset of symptoms or intermittently when suffering from acute respiratory infections Only one living patient had noted foul sputum in recent years Among those who died two were known to have had pneumonia and others may have had it hemoptysis was fairly common and fetid sputum was present in four

Of the living patients only one had clubbed fingers at the time of diagnosis but the sign was absent at the final follow up examination Physical signs were rarely absent at the time of diagnosis and persisted as a rule throughout the follow up period At the time of bronchographic diagnosis abnormal roentgen findings were present in all patients who subsequently died and in most of the others Comparative study of the earliest and latest films of each living patient revealed that the roentgen abnormalities had cleared partially in 5 and had not changed materially in 22

Of the five patients who died of bronchiectasis or its complications four had extensive saccular disease severe symptoms and were raising foul sputum Three of the four appeared chronically ill and poorly nourished at time of diagnosis the other who had moderately extensive disease with moderate symptoms appeared to be in good health but died suddenly of acute bronchopneumonia two years later After diagnosis of bronchiectasis at least three of the patients who subsequently died were hospitalized because of severe respiratory illness on one or more occasions before the fatal episode

Primary tuberculosis in children may produce asymptomatic bronchiectasis However among 30 patients of this group 17 had negative reactions to tuberculin This corresponds closely enough with the over all proportion of negative tuberculin reactions to warrant the conclusion that primary tuberculosis was not a frequent cause of bronchiectasis among the patients studied

mediums tend to create severe bronchospasm This was of considerable importance in the unsatisfactory films as manifested by incomplete filling secondary to the explosive effect of coughing However meticulous attention to topical anesthetization of tracheobronchial mucosa will improve the results with the water soluble agents

Two fatalities have been observed with these mediums in each case the methylcellulose base was thought responsible

Woman 53 showed on x ray examination of the chest a questionable enlargement of the right hilar area Bronchoscopy performed under topical cocaine anesthesia revealed nothing After premedication with 6 mg atropine and 50 mg sodium seconal® the tracheobronchial tree was anesthetized with 20 cc of 5% cocaine An intracutaneous test (0 1 cc) for sensitivity to diodrast® had a negative result Diodrast® (15 cc of a 50% solution in 1 75% methyl cellulose) was instilled into the right bronchial tree and roentgenograms taken Then 15 cc diodrast® was instilled into the left bronchus While films were being taken again she had a convulsion and respiration soon ceased Although the trachea was intubated and artificial respiration was given she died a half hour later At autopsy significant findings were confined to the lungs and were consistent with acute anaphylactic shock Although all drugs used are implicated various facts pointed to methylcellulose a the responsible agent.

In the second case the patient suddenly became cyanotic and collapsed 10 minutes after instillation of 15 cc of 50% urokon® in 1 75% methylcellulose At autopsy underlying sarcoidosis with bronchiectasis was found but death was considered the result of an anaphylactoid type of reaction

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BRONCHIECTASIS

Bronchiectasis as Seen in Ambulant Clinic Service A Follow up Study of 49 Cases over a Minimal Period of Nine Years Textbook descriptions of bronchiectasis as a crippling progressive disease contrast with the benign condition that is sometimes seen Anson McKim[3] (Ray Brook N Y State Tuberculosis Hosp) reports on 49 ambulant clinic patients observed for 9 20 years (mean 12 5 years) after bronchiectasis was discovered by bronchographic examination Eight patients died during the follow up period but three deaths were not attributable to bronchiectasis

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(3) Am. Rev T be c 66 457-476 October 195

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(3) Am Rev Tuberc 66 457-476 Oct be 1952

was it shown that the condition developed in a segment which seemed normal in preoperative bronchograms There was nothing to suggest that they had atelectasis or pneumonia after operation Of these 16 patients 9 had lingular bronchiectasis which had been present before left lower lobectomy and in 6 of these this was the only remaining bronchiectatic segment Finally 14 patients complained before and after operation of recurring attacks described as chest colds They probably had two diseases i e bronchiectasis and recurrent bronchitis

The following points are of importance in preventing disappointments complete mapping of the bronchial tree before resection ascertaining that the lingular segment has been properly mapped and that it is free from disease before left lower lobectomy alone is done and preparing the patient for residual symptoms where residual bronchiectasis is allowed to remain Finally recurrent bronchitis which may give persistent symptoms after eradication of bronchiectasis should not be overlooked

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NEOPLASMS

Mixed Tumors of Lung Reappraisal J L Ehrenhaft (Iowa State Univ) and Nathan A Womack[5] (Univ of North Carolina) report 14 cases In contrast to squamous carcinoma of the bronchus these tumors were found more frequently in women and in younger persons although never before puberty Symptoms are produced by bronchial obstruction and the resulting atelectasis with infection may be mistaken for pneumonia Bronchial obstruction may appear in episodes probably due to inflammation in the tumor with edema Apparently the tumor may be present for a long time growing slowly without symptoms until inflammation or ulceration is brought on by accidental aspiration of a foreign body or by respiratory infection Several tumors were discovered accidentally when a chest film was taken

Physical examination can reveal only those signs that are the result of bronchial obstruction Except for the round solitary peripheral lesion this is also true of the x ray findings When a major bronchus is involved (and this is the most

(5) *A n. S g* 136 90 110 *July* 195

Prognosis in bronchiectasis in respect to groups of patients may vary widely under differing circumstances. Bronchiectasis as encountered in military hospitals or ambulant chest clinics tends to follow a much more benign course than it does in patients seen on the wards of a large general hospital. Published opinions on prognosis and treatment are based exclusively on studies carried out in large general hospitals. Applied to medical practice outside such hospitals these opinions often prove to be unduly pessimistic and misleading. It is concluded that the prognosis and consequently the most desirable treatment for any individual patient can be decided only on the basis of thorough clinical study, often requiring a period of judicious observation. Treatment by pulmonary resection is of unquestioned value in many cases but surgery is not indicated whenever resectable bronchiectasis is discovered.

[As the author points out, the prognosis of bronchiectasis is often less grave than is stated in most textbook articles, in which the estimates of mortality are usually based on follow-up studies of hospitalized patients. Moreover, such studies date for the most part from before the era of antimicrobial therapy. Although McKim does not analyze the role of antibiotics and chemotherapy, there is little doubt that the periodic use of antimicrobial agents has reinforced the medical management of bronchiectasis. Other factors, such as earlier diagnosis, have probably also contributed to the more favorable prognosis. There is an impression widely reported that the bronchiectasis now seen is commonly less extensive than formerly. Statistics of prevalence are not available, but comments of others and our own impressions are that bronchiectasis is altogether less frequent than 10 or 15 years ago. This could be because of the more successful treatment of bacterial pneumonias of all types in recent years.—Ed.]

Disappointing Results of Pulmonary Resection for Bronchiectasis. John F. Paterson[4] (Toronto) attempted to determine why results of resection, which is an excellent treatment for bronchiectasis and the only means of permanent cure, are disappointing to some patients. Among 119 veterans aged 18-48 so treated there was only one postoperative death. Of 104 who were followed, 58 were completely satisfied with results, 24 partly satisfied and 22 completely dissatisfied.

Reasons for disappointment were investigated in 38 patients. Four were dissatisfied only because they had pain in the chest, described as a deep seated ache beneath the scar, coming on usually after exertion. Three were dissatisfied because thoracoplasty had been necessary for empyema after operation and two because pulmonary tuberculosis developed. Sixteen patients still had bronchiectasis. In only two of these

(4) Canad. M. A. J. 66:433-434, May 1952.

that these tumors originate in malformed lung tissue Because of their morphology and their clinical picture which differs from bronchogenic carcinoma the separate classification of mixed tumor is justified

Woman 44 had wheezing in left side of chest for 18 years and hemoptysis increasing shortness of breath and frequent attacks of pneumonia in the left lung for 12 years Broncho copy revealed a mixed tumor of the bronchus Resection of the left lung showed the mass to be extrinsic to the bronchus Since a few regional lymph nodes were involved all the lymph nodes in the area were resected



F g 18 — R g l l mph nod pl ed by m ta tat c t mor Ep th l l ll b th app f th on en n o t ll a om (C te y of Ehr haft J L nd W mak N A A n S g 136 90 110 J ly 1952)

Micro copic examination of the tumor showed a varied picture (Fig 17) There were nests and cord of cells in the classic pat tern often seen in mixed tumors Scattered diffusely throughout the tumor however areas of bone both membranous and endochondral in type without apparent relationship to the bronchial wall were noted In many areas adjacent to the bone there were collections of fat Other portions of the tumor showed chaotic conglomerate mas es of smooth muscle This muscle tissue apparently was well differentiated as was the bone The lymph nodes showed extension of the tumor as cancer and here epithelial cells were growing in sheet formation identical with the picture seen in oat cell cancer of the lung (Fig 18)

frequent site) the bronchogram usually shows occlusion and the tumor can be verified by bronchoscopy Examination of sputum for cells has been without value even for large metastasizing tumors

Local invasion has been found in many of these lesions Regional lymph node extension as well as distant blood stream metastases also occur Metastases often were identical to the more classic pulmonary cancer forms Metastases were never



Fig 17—Phot m og aphs d monst t g va d p ct e of t mo (C tesy of Ehre b ft J L and Wom k N A Ann. S rg 136 90 110 July 1952)

seen in a young person The greater the time lapsed since the first symptom and the larger the size of the tumor the more likely is the chance of regional and distant metastases

In this lesion there are groups of cells usually epithelial in type and showing decided resemblance to each other but growing in odd architectural patterns and tending to permeate or invade Ordinarily the mesenchymal framework is composed of reticulum and lined with cells resembling and functioning as endothelium The endothelial cells line huge sinusoidal spaces filled with blood into which the epithelial cells project This mesenchymal tissue may be much denser showing collagen formation or there may be bone or cartilage or even smooth muscle Such mesenchymal tumors have been called chondromas or hamartomas In the authors experience they have never been composed purely of the classic mesenchymal structures for they always contain epithelium It is believed

tario) in the light of five proved cases A sixth patient still alive has a presumptive diagnosis There were four men and two women aged 47 80 Signs and symptoms were those of a chronic pulmonary disease and not peculiar to this type of tumor Cough usually with little expectoration pain in the chest dyspnea wheezing respirations and weakness were com mon Pleural effusion was present in four cases Clinical course seemed much shorter than in other cases of untreated malig



Fig 20 —\ d l f p lm y d m t losely mbl 1 gz kt n heep d d f m × 121 (Court y f F h J H d H ll W J A.M A A h P th 55 16 170 F b y 1953)

nant pulmonary neoplasm None of the patients received x ray therapy Four were dead within three months of onset of symp toms In all increasing dyspnea was a prominent symptom With the widespread tumor growth lining innumerable pul monary alveoli in both lungs serious interference with normal pulmonary function is to be expected This was thought to be an important contributory cause of death Evidence of right heart failure was not observed

X ray findings in the chest were not pathognomonic of this disease However in all cases but one chest films re vealed a scattered densely mottled infiltration of both lung

[These tumors for which the authors reaffirm the title mixed tumors of the lung which was given to them 15 years ago by Womack and Graham (Arch Path 26 165 1938) are still more commonly designated by the term adenoma of the bronchus or are called chondromas or hamartomas when mesenchymal elements are predominant These more commonly used names do not signify the now generally recognized malig nant potentialities of these tumors which differ nevertheless in clinical behavior as well as in morphology and probably in origin from the more common types of bronchogenic carcinoma The usual designation will probably continue to be by the older title of adenoma which though less accurately descriptive than the authors designation at least retains the distinction from the typical bronchogenic carcinoma When these tumors are included in follow up statistics as carcinoma of the lung whi h is sometimes done the survival rates are thereby favorably influenced be cause the mixed tumors are usually slow to metastasize and they may exist for many years without exhibiting their malignant characteristics —Ed]

Primary Alveolar Cell Carcinoma of the Lung is discussed by John H Fisher and W J Holley[6] (Univ of Western On



F'g 19 – Roentg gr m h w g w d ly tt d fi ly mottl d filt t on f both l g (Court y f F l J H a d Holl y W J A M A A h P th 55 16 170 Febr ary 1953)

(6) A M A A ch P th 55 162 170 Feb ary 1953

symptoms may more readily have recalled previous respiratory attacks than other patients The data were not accurate enough for an etiologic relationship to be postulated

Seven (0 5%) of the 1 357 men with carcinoma of the lung and 40 (37 0%) of the 108 women were nonsmokers The corresponding figures for their paired controls were 61 (4 5%) men and 59 (54 6%) women Of the men with lung carcinoma 25 0% reported that they had been smoking before the onset of illness an average of 25 or more cigarets (or the equivalent in pipe tobacco) a day as compared with 13 4% among the controls For the women these proportions were 11 1% for the carcinoma group and 0 9% for the controls Estimated death rates for Greater London indicate that the mortality from carcinoma of the lung may increase in approximately simple proportion with the amount smoked Among men 45 64 the death rate in nonsmokers was negligible whereas in the heavier smokers it was estimated to reach 3 5 deaths/ 1 000 living/year

The association between smoking and carcinoma of the lung appears real It cannot be said however that tobacco smoke contributes to the development of all lung carcinoma that it is the sole cause for recently increased death rates nor that it can wholly explain the different mortality rates between town and country

[This authoritative statistical study presents overwhelming evidence regarding the association between smoking and carcinoma of the lung The authors do not argue that this is the sole cause of the increased incidence of pulmonary carcinoma In the following study Stocks gives evidence that atmospheric pollution is another factor and suggests that the effects of the two may be additive Not much comfort for the heavy smokers especially if they are city dwellers —Ed.]

Endemiology of Cancer of Lung in England and Wales According to P Stocks[8] mortality due to lung cancer (carcinoma and other malignant neoplasms of the bronchus lung and pleura) in England and Wales based on statements made on death certificates increased during the 10 years preceding 1945 more rapidly among men than women over age 35 The increase was relatively greatest among men aged 55 75 During 1911 20 certified mortality of men was about 1 7 times that of women but the sex ratio increased steadily for each decade over age 35 until in 1945-49 it exceeded 7 at ages 45 65 and reached 4 7 at ages 35-44 and 65 74 Statistics for 1921 39

(8) Brit J C 6 99 111 J 195

fields for which miliary tuberculosis pulmonary mycosis and carcinomatosis were considered as possible diagnoses (Fig 19) In the other case pulmonary adenomatosis was suggested on the strength of the x ray picture

All the tumors were malignant, producing regional or distant metastases and involved both lungs Three tumors were the multiple nodular type and three combined nodular and diffuse Histologic structures of the two anatomic forms of tumor were identical In structure and biologic behavior the tumors resembled carcinoma Structures believed to be cilia were associated with the tumor cells in one case only three others have been reported in which cells of this type of tumor have been ciliated In another case some of the tumor nodules closely resembled the histologic picture of jagziekte in sheep (Fig 20) The authors believe that these tumors arise from terminal bronchiolar epithelium Others have called them cancerous pulmonary adenomatosis

Study of Etiology of Carcinoma of Lung Richard Doll and A Bradford Hill[7] (Med Res Council) report on interviews conducted by four investigators among nearly 5 000 hospital patients The study covered hospitals in London Bristol Cambridge Leeds Newcastle upon Tyne and (for a limited purpose) the rural areas of Dorset and Wiltshire during 1948 52 Main comparisons were between 1 465 patients with carcinoma of the lung and an equal number of matched control patients of the same age and sex but with other diseases The controls so far as possible were in the same hospital concurrently with the lung carcinoma patients Distribution among social classes in the two groups was similar No association suggesting an etiologic agent of likely general significance was found between any type of occupation and lung carcinoma 23 0% of the lung carcinoma patients and 21 5% of the controls had lived near a gasworks for a year or more Use of coal gas or electric fires or other forms of heating in homes did not differ appreciably Fewer patients with lung carcinoma lived or had lived in the countryside

Lung carcinoma patients gave histories of previous attacks of pneumonia and chronic bronchitis oftener than patients with other forms of cancer Detailed analysis of the data suggested however that lung carcinoma patients with respiratory

(7) B M J 2 1 71 1286 D 13 195

there was a large range of mortalities for individual towns because of individual factors However there appears to be a general tendency for lung cancer mortality to increase with the total number of chimneys until the dwellings exceed 100 000 after which some other factor (population density) must be invoked to account for the high rates in London Manchester and Merseyside Whatever may have been the difference in completeness of diagnosis and certification 20 years ago it could hardly now account for such definite relations between lung cancer death rates and the extent and density of built up areas nor can it be supposed that people smoke twice as much tobacco in large towns as in small ones The facts seem to support the hypothesis that atmospheric pollution by smoke is an important factor on which tobacco smoking is superimposed

If domestic smoke is important one would expect to find in Greater London if there was no wind at all the highest incidence of cancer at the center with diminution in all directions outward Meteorologic records show that in Greater London during half of 1950 wind came from the quarter circle distributed around WSW whereas from the reverse quarter distributed around ENE the wind blew for only one sixth of the time The expected effect of that on smoke density would be to shift the maximum some distance from the center in a direction ENE and that is what the black patch in Figure 21 shows

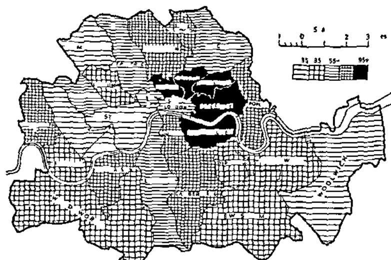
The total contribution of tobacco smoking to lung cancer incidence cannot be deduced from the relative frequencies found among nonsmokers and smokers in Greater London alone an area studied in a recent investigation It will be necessary to do similar studies among residents of rural areas where it is conceivable that smoking does not begin to show an appreciable relation to incidence of lung cancer until the number of daily cigarets is at a higher level than in London

Bronchial Carcinoma Presenting as Arthralgia Articular and periarticular pathologic conditions such as clubbed fingers are classic symptoms in chronic diseases of the heart and lungs Less known are arthralgia and hypertrophic pulmonary osteoarthropathy (Bamberger Marie disease) as the presenting symptoms in pulmonary malignancy Jens L Hansen[9]

(9) A t m d d (p 66) 14 467 47 1952

and 1940 46 for county boroughs (large towns other than London) and the rural districts showed that at ages under 35 the sex ratio was virtually the same in each class of area and did not increase At ages 45 65 it was considerably greater in the towns than in rural areas in both periods and it increased in both types of area between 1921 39 and 1940-46

Recent investigations have pointed to tobacco smoking as a possible cause Stocks suggests that atmospheric pollution may be an additional factor From Figure 21 it is seen that



F g 21—M p f Lo d d m t pol tan b rough sh w g 1946 49 d th d e t e ot th l b h d pl m l /100 (l l t d by applying tes f Engl d d W l s t p p lat at age 0 35 45 55 65 75+) (C rte y f Stocks I B t J C n o 99 111 J 195)

mortality incidence for 1946 49 varied widely in various areas of metropolitan London The differences shown are large and although they are positively correlated with the old social class and density per room indexes based on the 1931 census they cannot be so explained

If lung cancer is caused in part by atmospheric pollution through smoke from domestic chimneys the rate would be expected to increase as the total number of inhabited dwellings in the vicinity increases The rate should also be positively correlated with the density of dwelling units per acre Within groups of towns having less than 50 000 occupied dwellings

bone metastasis being excluded) In seven bronchial symptoms were present from the onset Only in the four cases mentioned previously was arthralgia the presenting symptom Resection was done in 56 cases in 5 of which arthralgia was present Thus arthralgia was present in about 10% of cases whether the tumor was resectable or not

The pathogenesis of these arthralgias is obscure they are probably caused by reflexes rather than by circulatory disturbances and stasis in the lungs

The joint symptoms in bronchial carcinoma manifesting themselves as hypertrophic pulmonary osteoarthropathy resemble but are not identical with the finger symptoms seen in chronic diseases of the heart and lungs In the latter diseases pains in the large joints do not predominate and disappearance of clubbed fingers after cure of bronchiectasis is far slower than the dramatic response of joint pains to removal of a lung tumor hippocratic fingers are a long time in developing and may persist for years without extension of the condition to the large joints Bamberger Marie disease in pulmonary cancer develops within a few months and is not always accompanied by typical hippocratic fingers articular symptoms in certain cases of localized pulmonary suppuration take the same course as those in carcinoma The Bamberger Marie and the Hippocrates type of arthralgia are undoubtedly closely related The pathologic anatomy is identical (thickening of periosteum and soft tissues) there are clinical types from one extreme to the other and in many cases both have developed

[Instances of hypertrophic pulmonary osteoarthropathy involving the large jo ts of tl e extremities and simulat ng arthritis as the presenting symptoms of pulmonary cancer are not rare The incidence here reported is less than that r po ted by Alvarez (J A M A 140 364 1948) from Argent na but accords well with North American experience. Since the joint manifestations characteristically occur early and frequently in association with the most resectabl types of pulmonary cancer the importance of the association is self evident Bamberger Marie di ease (hypertrophic pulmonary osteoarthropathy) secondary to pulmonary malignancy should therefore always be thoi ght of in patients with joint pain and be excluded by appropriate x ray examinatior s of the chest and of the extremities —Ed]

X ray Therapy and Carcinoma of Bronchus Analysis of Effect on 218 Patients of Irradiation of Primary Lesion with at least a two year follow up is presented by D E Meredith Brown[1] (St Bartholomew s Hosp London) About half im

(1) B t J R d l 25 472-475 Sept mbe 1952

(Copenhagen) reports four cases The clinical course of Cases 1 3 was strikingly uniform The lung tumor caused no respiratory symptoms and was discovered accidentally In Case 4 joint symptoms started two months before respiratory symptoms Each patient sought aid for articular pains Moderate and continuous fever was present in Case 1 high and recurrent fever in Case 3 and fever for a short period in Case 4 The sedimentation rate was elevated from 70 mm /hour (Cases 1 and 2) to 120 mm /hour (Cases 3 and 4) Joint symptoms were symmetrical and polyarticular and affected mainly the large joints at first and the fingers later The joints were tender and showed periarticular swelling but no intra articular effusion Motion was limited to 60 80% Roentgen examination revealed slight osteoporosis in the articular ends of the bones and periosteal thickening of the fingers in Cases 1 and 3 Antistreptolysin titers and white blood cell counts were not remarkable The general condition of all four patients was poor Two (Cases 1 and 3) could hardly leave their beds perhaps due to fatigue weight los and joint pains The tumor was limited in three cases and could not explain the exhausted general condition

In Cases 1 3 in which the tumor was resectable there was a squamous cell carcinoma with aseptic necrosis in two and peripherally accumulated pus in the other In Case 4 in which an exploratory thoracotomy was done oat cell carcinoma was found Macroscopically the tumors represented all the usual types of bronchial carcinoma parenchymatous (Case 1) segmental bronchial (Case 2) lobar (Case 3) and central (Case 4) The articular symptoms disappeared within few weeks after surgery In the cases with resection no recurrence of arthralgia was seen in the observation period (nine months to two years) In Case 4 joint symptoms returned five months after operation Improvement in the first week after operation was most striking All pains disappeared and most of the motion returned Swelling decreased more slowly than the other symptoms the circumference of the fingers and knees remaining nearly unchanged for the first month Two or three months after operation the circumference of the knees had in all cases decreased 1 2 cm

Revision of the records of 100 cases of bronchial carcinoma showed 8 further cases with articular symptoms (5 cases of

Donald W Spicer F William Dowda Merrill A Bender and William E Noel[3] report results in 16 patients most of whom were in a frankly terminal stage or nearly so The majority received one injection most doses ranging from 60 to 98 mc Several patients received more than one injection The response in general was encouraging Four patients obtained striking improvement both in reduction or cessation of fluid accumulation and in relief from pain However relief lasted only 2½ weeks in one of the patients and death soon followed Another died four months after treatment without requiring further taps Four patients experienced moderate relief the intervals at which taps were required being considerably lengthened In the two who are still living taps have not been necessary for 2½ and 3½ months respectively

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BRONCHIAL ASTHMA

Serial Courses of Corticotrophin or Cortisone in Chronic Bronchial Asthma Robert P McCombs[4] (Tufts College) reports results in five patients with chronic intractable asthma treated with repeated courses of corticotrophin (ACTH) or cortisone Symptomatic measures constituted the only other treatment When the hormones were given in sufficient dosage soon after recurrence of asthma incapacitating attacks were avoided and an asymptomatic state was restored Remissions however were of short duration and retreatment was necessary on the average of once a month or less The intermittent use of the hormones helped avoid the unpleasant side effects often associated with prolonged therapy

Corticotrophin seemed to bring about more uniform beneficial results than cortisone although cortisone definitely caused improvement in many instances A long acting preparation of corticotrophin in gelatin gave the best results and required the smallest dosage

In properly selected and supervised cases this form of therapy is practical In the long run it might prove less expensive than other medication and emergency medical care including hospitalization

(3) Am J Roe tg 1 68 413-4 0, Sept mbe 1952
(4) N w E gla d J M d 247 1 J ly 3 195

proved symptomatically after treatment but less than one fifth lived longer than a year Age made no difference in the course of the disease The histologic picture had some bearing and as expected patients with anaplastic lesions had the greatest chance of immediate benefit but a slightly worse prognosis Patients with symptoms for longer than six months had more chance of surviving nine months than those with a shorter history When the neoplasm was in an upper lobe bronchus the immediate and ultimate outlook was slightly more favorable No appreciable difference in results was found by varying the number or the size of the fields nor with the different kilovoltages used but few patients showed immediate improvement with less than 2000 r and the survival rate was definitely improved when doses of over 4000 r were given

Considerable alleviation of mediastinal obstruction is afforded by x ray therapy and distressing hemoptysis is almost constantly stopped Supervoltage therapy seemed preferable especially for patients with mediastinal obstruction

Results of Radiation Therapy for Bronchogenic Carcinoma Statistical Analysis of 125 Cases is presented by Bernard P Adelman (Temple Univ) In this group adequate radiation was directed toward the primary lesion There was no correlation between sex age at onset of symptoms or duration of symptoms and prognosis Patients with undifferentiated carcinoma had the shortest survival time after therapy (5 5 months) and those with adenocarcinoma the longest (8 months) Patients with squamous cell carcinoma occupied an intermediate position (7 1 months) However if two patients with adenocarcinoma who survived for about two years are excluded average survival for this group was only 3 3 months Twenty two patients survived more than 12 months after therapy Of these 15 had squamous cell lesions 2 undifferentiated carcinoma and 2 adenocarcinoma Two growths were classified only as malignant tumors and one as bronchogenic carcinoma type indeterminate The tumor dose varied from less than 1000 to more than 6000 r Statistical analysis of results indicated that little clinical benefit in terms of increasing survival will result from increasing tumor doses

Use of Radioactive Colloidal Gold (Au^{198}) in Pleural Effusions and Ascites Associated with Malignancy E K King

( ) R d l gy 59 383 398 S pt b 195

Fatal Anaphylaxis in Bronchial Asthma Following Administration of Penicillin Report of Two Cases with Autopsy Findings is presented by Theodore J Curphey[6] (Hempstead N Y)

Woman 43 had a sore throat and frontal headache Moderate infection of the pharynx was noted but the lungs were clear on auscultation She was given 300 000 units procaine aqueous penicillin intramuscularly within a few minutes breathing became stertorous and she died She had had severe bronchial asthma for years During the previous five years sh had received many injections of penicillin for occasional attacks of pharyngitis She had repeatedly received aqueous procaine penicillin without ill effect but there was a history of allergy to penicillin in oil

The other patient was given penicillin while having symptoms of asthma Symptoms became aggravated immediately convulsions developed and the patient died Such fatal reactions are admittedly rare and despite the coincidence of observing two such cases in a relatively short time in one community evidence suggests that considerable care should be exercised in administering any antibiotic to patients likely to be hypersensitive

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PNEUMOCONIOSES AND OTHER INHALATION DISEASES

Etiology of Corundum Smelter's Lung (Bauxite Worker's Lung, Shaver's Disease) In 1947 49 papers were published in Canada and Germany dealing with pulmonary disease (occasionally fatal) acquired in the electrometallurgical production of corundum from bauxite Horst Gartner[7] (Saar Univ) compared Canadian and German experience In Canada disease incidence and deaths occurred principally in four plants in the area of Niagara Falls Ont where 350 workers were exposed 35 of them fell sick and 10 died In addition x ray examination of 46 showed early pulmonary changes Exposure time averaged about six years indicating a variable susceptibility Nine patients had spontaneous pneumothorax At autopsy diffuse fibrosis wa found in the thickened alveolar septa which showed a cuboidal epithelial layer The air spaces were compressed and filled with phagocytes giant cells and detritus

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(6) New York J Med 53 1107 1110 May 1 1953
(7) A M A Arch Ind Hyg 6 339 343 October 1952

Role of Cortisone in Treatment of Severe Bronchial Asthma is discussed by Walter S Burrage and John W Irwin[5] (Massachusetts Gen l Hosp) The hormone is of value in providing rapid symptomatic relief in the patient of unknown background found in status asthmaticus if the usual measures fail The authors have used the following dosage 300 mg in divided doses the first 24 hours 200 mg daily until improvement is marked and then 100 mg daily until asthma clears In certain cases cortisone may not give relief and may even fail to be lifesaving

Patients with severe pollen asthma usually respond to hospitalization and conventional therapy but attacks frequently recur on discharge unless the pollen season is over Cortisone can hasten recovery and reduce hospital stay It may also be continued in maintenance doses thereby keeping the patient asthma free until the end of the pollen season

In some patients with asthma it is often impossible to incriminate any specific antigen or group of antigens Asthma of this type often first appears in the fourth decade In some patients it becomes so persistent that long periods of hospitalization are often necessary and the patients are never really free from asthma despite intensive conventional treatment Fourteen such patients were restored to a useful life with cortisone

Dosage varies with each patient In general enough hormone must be prescribed initially until relief from all symptoms of asthma is obtained daily dosage is then reduced to a minimal level that will maintain freedom from wheezing If on a lowered dosage asthma returns or becomes more severe larger doses are indicated (it has often been found advisable to return to initial high doses and then to reduce the amount gradually to a suitable maintenance dose) No patient was kept asthma free on less than one 25 mg dose of cortisone daily Once the optimal daily dose was established its level did not seem to fluctuate materially either up or down Complications and undesirable effects were minimal during many months of cortisone therapy *but strict supervision is essential* for success

(5) New E gland J Med 248 679 68 Ap 16 1953

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(6) N w Y k J Med 53 110 1110 M y 1 1953
(7) A M A A h I d st Hyg 6 339 343 Octobe 195

The Canadian authors are still uncertain as to the cause seeming to assume a kind of chemically irritating effect

In a plant in the Rhineland 15 disabilities and 8 deaths have been reported all in workers exposed to fumes from electric furnaces in which corundum was made from bauxite Dense fume clouds were noticed over the furnaces particularly during wartime when ventilation was insufficient because of blackout regulations Pulmonary *diseases among corundum smelters* like aluminum lung disease seem to have resulted from the more difficult working conditions of wartime Cases in workers with predominantly postwar exposure are not known to the author In Germany the period of exposure to fumes was 6 16 years The disease started with shortness of breath or spontaneous pneumothorax and with increasing difficulty in breathing was fatal in several cases within one to two years More than half of the patients who died had active tuberculosis a complication not reported in the Canadian literature However this should not be overemphasized as the smelters worked in close contact in a small workshop where they probably infected one another Pathologic findings did not differ fundamentally from those described by Canadian authors

Gamma alumina presumably formed in the smelting of bauxite has been suggested as the causative agent The author feels that this contention has not been adequately proved His research revealed presence of corundum bauxite amorphous silica and mullite in both plant dust and dust from diseased lungs Since corundum is harmless and bauxite is not known to be noxious *only mullite and amorphous silica have to be* considered as the disease producing agents *On the* basis of results of animal experiments with amorphous silica and of reports on injury caused in the production of ferrosilicon in which the importance of amorphous silica was stressed the author suggests that silica may be the primary agent and mullite a contributing factor

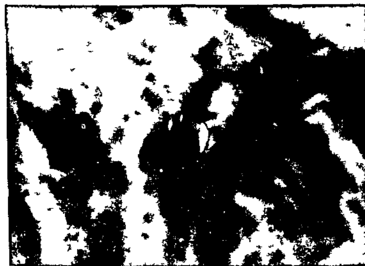
Pulmonary Talcosis with Involvement of Stomach and Heart Report of a Case is presented by William E Jaques and Kurt Benirschke[8] (Harvard Med School)

Man 42 had come in contact with talcum powder in 1936 42 In 1943 he was hospitalized because of cough dyspnea and weakness Chest roentgenogram was suggestive of silicosis showing coarse streaky areas involving the upper two thirds of each lung and spar

(8) A M A A b I d t Hyg 5 451 463 May 1952

ing the extreme apexes and bases The left upper lobe presented a honeycombed appearance suggesting bronchiectasis The heart and hilar lymph nodes appeared normal Hand and feet revealed no radiologic sarcoid like lesions The disease progressed signs of cor pulmonale appeared and the patient died in 1950 The radiologic appearance of the lungs changed little during this interval

At autopsy the right atrium and ventricle were dilated and coronary arteries howed atherosclerosis The deeper portions of the lungs were very firm fibrous and in some areas nodular On section these firm areas pre ented a mottled grayish appearance and from



F g —L g ly 75% p l d Cryt l f t l b p mp ed bl k th t b k d H m t yl d l t m × 100) (C rt y J l W E d L hk K A M A A h l d t H g 5 451 463 M y 195)

them a moderate amount of blood could be expres ed There wa an extensive atheromatou process in the pulmonary arterie The other organs sho ved no gro s changes Micro copically there were pulmonary granulomato i and fibrosis polaroscopic examination of all lung section revealed scattered needle shaped crystal varying from 1 to 10 μ (generally 2 to 4 μ) in length and a fraction of 1 μ in thicknes (Fig 22) The crystal were occasionally se n in phagocyte but not in the granuloma Granulomas were also noted in the stomach epicardium and myocardium although these did not contain any cry tal no granuloma were found in any other organ A po sible m ch ni m for the heart and stomach lesions is that of a hyperergic ho t r action

Berylliosis Summary and Survey of All Clinical Types in 10 Year Period Joseph M DeNardi H S Van Ordstrand and George H Curtis[9] (Western Reserve Univ) report 461 cases of various types of beryllium poisoning

Dermatitis was usually confined to exposed parts of the body but in sensitive patients became generalized Lesions varied from diffuse papules and vesiculopapules to macules and irregular areas of edematous lesions with or without vesicle formations Most common symptoms were a burning sensation and pruritus of the affected parts Usually there was concomitant involvement of conjunctivas and eyelids Response to treatment varied patients exposed to the fluoride compound being most refractory but recovery usually was complete 7 14 days after removal from exposure Therapy consisted of immediate avoidance systemic administration of antihistamines and application of mild antipruritic and antihistaminic ointments Dermal manifestations were with few exceptions caused by contact with soluble forms of beryllium principally the fluoride and the sulfate Of 209 patients with acute dermatitis 63 had been exposed to beryllium in sufficient concentration for it to act as a primary irritant and produce an immediate contact dermatitis whereas 146 had the eczematous type of dermatitis often a severe manifestation as the result of acquired sensitization attributed to longer exposure to smaller concentrations Beryllium ulcer usually an acute localized manifestation due to implantation of crystals of the soluble salts in a pre existing skin break often occurred concomitantly with contact dermatitis and pathologic findings were those of a severe skin reaction to a primary irritant Untreated lesions might persist for months Treatment consisted of curettage of the ulcer and removal of offending inclusions

Acute tracheobronchitis present in 129 patients invariably was caused by inhalation of vapors dusts and mists of BeF NH_4BeF_2 or $BeSO_4$ Onset was rapid or insidious depending on the magnitude and duration of exposure Symptoms were productive cough substernal discomfort and moderate exertional dyspnea Normal temperature decreased vital capacity with varying degrees of dyspnea injection of the nasopharynx limitation of chest expansion and sibilant rales in the hilar and

(9) Cl v l d Cl Q art 19 171 193 O t be 1952

basilar areas of the lungs were found Chest roentgenograms might show increase of bronchovascular markings Therapy was not specific All patients recovered usually in one to four weeks

Acute chemical pneumonitis was caused by inhalation of vapors mists and dusts of BeF $BeSO_4$ combinations of the soluble salts and BeO of high specific area prepared at relatively low calcining temperatures Two types were encountered i e fulminating and insidious depending on magnitude and duration of exposure Symptoms of fulminating pneumonitis usually occurred approximately 72 hours after brief but massive exposures whereas the insidious form manifested symptoms several weeks after prolonged exposure to lesser concentrations Symptoms were progressive rarely productive spasmodic cough progressive dyspnea with tightness of the chest and substernal pain or discomfort anorexia with ensuing weight loss general malaise and weakness Objectively there were varying degrees of decreased vital capacity with severe dyspnea *rapid pulse and acro yanosis hyperemia of the naso* pharynx no fever limited chest expans on with rales principally in the lower lobes and hilar areas Chest roentgenograms became positive one to three weeks after onset of symptoms and varied with stage and intensity of the disability Findings in chronological sequence were diffuse bilateral haziness usually of the lower lung fields followed by irregular soft parenchymal infiltration and finally discre e or conglomerate nodules Therapy wa not specific Recently cortisone and ACTH have been used with some success Of 93 patients with acute chemical pneumonitis 10 died all others recovered except 1 who had pulmonary fibrosis and decreased vital capacity none had the chronic or delayed form of berylliosis

Chronic pulmonary granulomatosis or berylliosis is a generalized disease characterized by pulmonary insufficiency Major pathologic changes occur in the lungs the granuloma being the most characteristic lesion Onset which may occur from a few months to several years after initial exposure is insidious with a nonproductive cough chills and fever anorexia with asthenia and loss of weight progressive exertional dyspnea with substernal pressure and bizarre thoracic pains Objective findings were varying exertional dyspnea increased pulse rate decreased vital capacity watch glass finger nails

or clubbing of fingers acrocyanosis decreased thoracic expansion and crackling rales throughout both lung fields in the advanced stages Routine and special laboratory procedures failed to reveal any specific common abnormal findings Serial chest roentgenograms revealed a transition from a generalized ground glass or granulation of the parenchyma in the early stages of the disease to the late phases of nodulations emphysematous changes and cor pulmonale Treatment was symptomatic Cortisone and ACTH were given in the aggravated state of the disease and to patients showing progression of symptoms Thirty one patients were observed In 12 the disease was nonoccupational occurring in people living within a 1/4 mile radius of beryllium plants Approximately 50% of the 31 patients were static or showing some improvement 15% were showing progressive regression and 35% died

Chronic beryllium granuloma is a subcutaneous lesion usually the result of implantation of beryllium phosphor (zinc beryllium silicate) in a skin laceration or puncture produced by a broken fluorescent tube Lesions are always localized or self limited and usually appear one to four months after implantation of the phosphor A subcutaneous nodule forms which may eventually develop central necrosis and subsequent surface drainage Treatment was thorough cleansing and debridement of fresh wounds and adequate wide surgical excision of existing granulomas In two cases microscopic changes were identical with the pulmonary granulomas described in chronic pulmonary berylliosis

Presence of beryllium in body tissue and urine indicates past or recent exposure The amount detected by analytical methods had no relation to existence or severity of specific disease process Beryllium remains in body tissue and is excreted for many years after removal from exposure without evidence of beryllium poisoning There was some evidence of decrease of excretion of beryllium proportionate to increase of time from last exposure

In recent years the incidence of cutaneous berylliosis among workers in the beryllium industry has been reduced from 25 to 2% and respiratory syndromes have been almost entirely eliminated by engineering and medical hygienic preventive measures

[Because of the sometimes long latent period—up to 10 years—in the chronic pulmonary form of berylliosis this diagnosis mu t still be con sidered in diffuse pulmonary granulomatosis despite the recent advances in preventive measures —Ed]

PULMONARY MYCOSES

Mycotic infections of the lung or the pulmonary manifestations of generalized mycotic infections are becoming of ever increasing importance in the differential diagno is of acute and chronic pulmonary disorders The pulmonary as well as the extrapulmonary manifestations are often as diverse as those of tuberculosis and the clinical diagnosis as the follow ing group of abstracts illu trates is usually d fficult even when the pos sibilities of mycotic diseases are thought of Advances in therapy make it a matter of urgent importance however that these specific diagnoses be made —Ed

Actinomycosis of Lung Etiology Diagnosis and Chemo therapy According to Lawrence P Garrod[1] (Univ of Lon don) actinomycosis in all its forms is much commoner in men than women and although it can occur at almost any age is seen most often in young adults The mouth is believed to be the source of infection It is usually assumed that the organism reaches the lung by aspiration but it is conceivable that a mycotic embolus is carried by the blood from an oral focus to the lungs The lesion is usually in the lower lobes and con sists of foci of suppuration with surrounding dense fibrosis By direct extension it commonly involves the pleura or chest wall and usually it is only when this has occurred that the disease is suspected

Pus is the material on which a laboratory diagnosis of any form of actinomycosis must almost always be based In thoracic disease sputum is an alternative but its examination is rarely helpful Unless actinomycotic granules are present it is doubtful whether a diagnosis should ever be based on sputum findings The mere presence of branching mycelium in films or the cultivation of an actinomyces may be due sim ply to contamination by the flora of the mouth Even exam ination of bronchoscopic specimens hardly eliminates this possible fallacy The flora of any cavitating lung lesion is apt to be mixed and is composed largely of oral types There seems to be no reason why some of these should not be leading a purely saprophytic existence in a lung cavity as they do in the

(1) T b 1 33 58 66 S pt mbe 1952

mouth the mere existence of an actinomyces in bronchial secretion is no proof of actinomycosis

Empyema more or less localized has usually formed be fore the disease *is suspected and pus is therefore available for* examination This material is highly characteristic when there is enough of it for its features to be properly appreciated a swab specimen is not enough for this purpose In bulk it has an offensive but not distinctive odor Its absolutely diagnostic



F g 3—C u h d g le fr m act n myc ti p s G am sta d d d from ×1000 (C t y of G od L P Tub r le 33 258 66 S pt mb 1952)

feature is the presence of so called sulfur granules which are colonies of the fungus These are in fact not yellow but dull white by reflected light and light brown translucent and re *fractile by transmitted light They are usually about 2 mm* in diameter sometimes smaller occasionally much larger and irregular but roughly spherical They may not be visible at all unless (1) the tube is rotated while held at an angle so that a thin film of the pus coats its inner surface in which they stand out well or (2) pus is shaken up with about five times its volume of water (the granules then settle rapidly to *the bottom of the tube)* Masses of other bacteria or small frag ments of caseous material tissue or fibrin may be confu ed with them although none of these has the same appearance to the experienced eye

If the object is removed crushed on a slide and gram stained the true granule will be seen to consist of thin gram positive branching mycelium either in complex coherent masses and staining well (Fig 23) or in smaller fragments with less obvious branching staining poorly and accompanied by many short lengths of gram negative mycelium resembling rod shaped bacteria These forms result from degenerative changes in older colonies Bacteria may also be seen especially if the lesion has been draining and thus become secondarily infected

In making cultures the author washes several granules in sterile saline—not in alcohol as some have recommended—and grinds them into a fine suspension a small loopful of which is sown on several plates of culture medium which are incubated for a week The surest way of inducing the organism to grow well is to give it a choice of several mediums The only condition which will permit the growth of every strain is complete anaerobiosis some strains either require or prefer added CO

Although the sulfonamides have a demonstrable effect on the disease penicillin is much more effective In one series 11 (79%) of 14 patients not treated with penicillin died whereas only 7 (22%) of 33 treated with the drug died Even among these seven most received amounts of penicillin inadequate by present standards Treatment with penicillin should be both vigorous and prolonged High concentrations of the drug are necessary first to penetrate areas of fibrosis and suppuration and then to penetrate the colony of the fungus itself a dense and substantial structure unlike the form assumed by any other micro-organism in the body Although information about sensitivity to other antibiotics is scant in vitro studies have shown sensitivity to terramycin chloramphenicol aureomycin and streptomycin in this order

Acute Blastomycotic Pneumonia Report of Fatal Case of 20 Days Duration. Roger D Baker George W Warrick and Ray O Noojin (Med College of Alabama) report a case that is unusual because of its short acute course and the absence of extrapulmonary complications

Woman 41 for 11 days had had cough fever and pain in the chest which had not responded to antibiotics and sulfonamides The

(2) A M A A h I t M d. 90 718 724 N mb 195

white blood cell count was 17 350/cu mm with 78% polymorphonuclears 20% lymphocytes 1% monocytes and 1% eosinophils Routine studies were not remarkable except that Staphylococcus albus resistant to most antibiotics except chloramphenicol was cultured from the blood A sputum smear revealed many gram positive cocci in clusters and many yeast forms Stereoscopic films of the chest showed the right and left lung bases to be cloudy obscuring the right and left borders of the heart and the outline of the right diaphragm Findings were interpreted as suggestive of pneumonitis of the right and left bases The patient did not respond to chloramphenicol and various other antibiotics

Significant autopsy findings were limited to the thoracic cavity (the skull was not opened) On sectioning of lungs yellowish white nodular consolidations were noted with greatest involvement of the right lower lobe and with a tendency to involve hilar rather than apical regions The cut surfaces were moist and exuded pus but no abscess cavities were seen Microscopic examination of the pus revealed Blastomyces dermatitidis and this organism was grown in culture In microscopic sections of lungs the blastomycetes were seen as thick walled organisms some of which were budding They were not found in any other organs

Blastomycosis is probably contracted through some form of contact with the fungus as it grows in nature but little is known of its natural habitat The disease has little or no tendency to spread from person to person Occasionally pathologists have contracted the cutaneous form In this patient the infection was primary in the lungs and it is unlikely that it represented a pneumonia secondary to cutaneous or other foci Twenty (22%) of 91 patients with the systemic form reported in the literature lived less than six months The mortality is high and of 59 proved cases of the generalized disease 49 died within five years Gross appearance of the lungs varies in acute cases suppurative pneumonia is found whereas in those of several months duration cavities are more likely findings Diffuse or focal consolidation and simulation of miliary tuberculosis may be present or larger nodules may be noted Thickening of the pleura may be a characteristic feature

In most cases of extensive systemic blastomycosis the patient s serum will fix complement with suspensions or extract of B dermatitidis The reaction is specific when positive Prognosis is best in a patient who has a positive skin reaction and a negative complement fixation reaction and poorest in a patient with a negative skin reaction and a strongly positive complement fixation reaction

The same organism B dermatitidis causes both cutaneous and systemic blastomycosis Cutaneous blastomycosis may frequently be cured particularly if therapy is begun before the lesions have become widespread the systemic disease is highly fatal Iodide therapy is usually effective but should not be given when the patient is hypersensitive to the organism as determined by skin test In such a case the hypersensitivity should be decreased artificially by administering gradually increasing doses of vaccine Additional use of x ray therapy and suitable surgical procedures may be indicated in treatment of cutaneous lesions In systemic blastomycosis surgical drainage of deep lesions is desirable Stilbamidine and propamidine have been reported as affecting favorably the course of blastomycosis

Case of Pulmonary Cryptococcosis is reported by D Barron Cruickshank and G Kent Harrison[3] (Cambridge)

Woman 50 had few symptoms except a cough persi ting for half



Fig 4—E i pec men how g t rulom m d ll l be wh h bulg to obl q fi w h d ff se p d t low lobe (Co rt y f Cru ksh k D B. d H so G K Th 7 18 184 J 1952)

(3) Th 7 182 184 J 195

a year after influenza Chest roentgenogram revealed an opacity in the right lung Bronchoscopy disclosed a rounded mass just inside the orifice of the middle lobe bronchus The bronchial aspirate and bronchial biopsy specimen contained numerous morphologically typical Cryptococcus neoformans There were no cerebral symptoms and the lumbar cerebrospinal fluid was normal A right pneumonectomy was successfully performed The excised specimen revealed a tumor like mass occupying the middle lobe with a diffuse extension to the basal segments of the lower lobe (Fig 24) The upper lobe was unaffected and there was no enlargement of the regional glands Histologically the tumor and extension consisted of a solid mass of cryptococci replacing the parenchyma and practically devoid of any supporting stroma it was surrounded by a fibrous capsule in which appeared lymphocytes and giant cells Six days after operation she died suddenly of embolism of the left pulmonary artery Before autopsy cerebrospinal fluid was removed by cisternal puncture and was found to be blood stained and loaded with cryptococci The brain showed some regions of indefinite degeneration and extensive study was required to demonstrate cryptococci in the subarachnoid layers of the medulla the only specific abnormality found Nothing significant was found in other organs

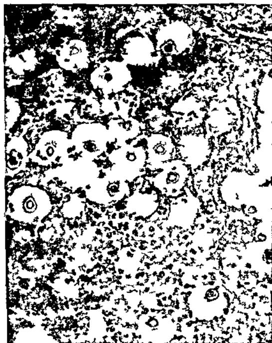
In the lung this disease may be tumor like (toruloma) bronchopneumonic or miliary it is usually progressive and ultimately initiates fatal meningitis This predilection for the brain meninges and lung taken in conjunction with symptomatology necessitates differentiation from tuberculous meningitis tuberculoma and pulmonary tuberculosis Since cerebral involvement is usually preceded by some pulmonary symptoms the lung is regarded as the usual portal of entry The disease is highly fatal affects people of all ages and women about twice as frequently as men Chemotherapy is disappointing and since the broad gelatinous capsule prevents antibody formation vaccine therapy also fails Two successful pneumonectomies have been reported

Torulosis (Cryptococcosis) Producing Solitary Pulmonary Lesion Report of Four Year Cure with Lobectomy To the five cases found on record Morris Berk and Bruno Gerstl[4] (V A Hosp Oakland Calif) add another

Man 30 had infrequent episodes of cough fever substernal tightness wheezing and malaise diagnosed as bronchial asthma Attacks were nonseasonal and each lasted about a week Five months before hospitalization a survey chest roentgenogram showed a spot but he continued to be asymptomatic until three days before hospitalization *entering with mild fever appearing* moderately ill but without any physical signs except localized rales Hemoglobin

(4) J A M A 149 1310 1312 A g 2 1952

content was 14 3 Gm /100 cc white blood cell count 18 700 with 72% polymorphonuclears and sedimentation rate 95 mm (Westergren) Bronchoscopic examination gave negative results The initial chest x ray revealed a density occupying the anterolateral and lower portions of the upper lobe of the left lung just above the interlobular fissure A subsequent x ray revealed some increase in size of this shadow with the addition of a small amount of pleural



F g 25 —C yptococcu g m l g le w th h t t truct d w l f l cap l l d f m ×230 (Co rt y f B k M d G tl B J A M A 149 1310 131 A g 2 195)

fluid Bone survey and excretory pyelograms were normal A bronchogram of the left side showed moderate cylindric bronchiectasis in the lingular region However bronchi extending to the lesion in question appeared normal

A tentative diagnosis of pneumonia was made and he was treated with penicillin and sulfadiazine but without response He continued to have fever (99 101 6 F) and on the eighth day after entry there was a sudden increase of pain in the left lateral portion of the chest with physical signs of fluid accompanied by a pleural friction rub

By thoracentesis 200 cc serosanguineous fluid with sediment showing numerous cells of endothelial character was removed A tentative diagnosis of tumor was made and the left upper lobe containing a large mass was excised The tumor on frozen section was diagnosed as mycotic granuloma The patient recovered uneventfully and was alive without evidence of recurrence or dissemination four years later

Sectioning of specimen showed an oval firm tumor like fairly well encapsulated grayish yellow mass 7 × 6 × 6 cm with a mucoid surface Sections representing the peripheral areas of the lesion revealed fairly dense connective tissue infiltrated by small round cell There were cellular debris and fine pink staining fibers with circular clear spaces containing round bodies whose light pink broad peripheral zone suggested capsule formation (Fig 25) The remaining pulmonary parenchyma was unremarkable

The lung may be the portal of entry of this highly fatal disease For this reason surgical excision is recommended as a curative measure before dissemination occurs Torulosis should be considered in the differential diagnosis of circumscribed nodular pulmonary lesions

Pulmonary Histoplasmosis Study of 22 Cases with Identification of Histoplasma Capsulatum in Resected Lesions is reported by Thomas F Puckett[5] (Fitzsimons Army Hosp) All patients were white nine resided in Panama for 24 39 months immediately before the lesions were discovered Almost all of the others had lived in areas known to be endemic for histoplasmosis immediately before or at the time the lesion was discovered

There was no typical clinical picture Six patients were asymptomatic Symptoms in the others included weight loss and chronic cough said to be nonproductive by most patients None had purulent and some had blood tinged sputum Much of the symptomatology was brought out by close questioning after the lesion was found by roentgenography Physical examination was noncontributory in all instances

Results of numerous routine blood and urine examinations were normal Five patients had elevated sedimentation rates All but one patient had positive reactions to histoplasmin skin tests results of tests with coccidioidin and PPD varied Results of complement fixation and colloidal agglutination also varied the highest titers were in patients with lesions which might be considered active histologically No positive complement fixations for Coccidiodes immitis were obtained Re

(5) Am Rev T be 67 453 467 Ap 1 1953

sults of these tests appear to indicate the relative inactivity of the lesions Until more experience is gained in use of serologic tests and standardization is effected caution should be exercised in their interpretation Diagnosis cannot be made with certainty from a history of endemic exposure a pulmonary lesion and a high titer although it can be strongly suspected

In one case only a hilar node was removed Pulmonary parenchymal lesions were present in all the other cases The lesions were separated into four groups (1) focal encapsulated pneumonitis with no satellite lesions (2) a large focus of encapsulated pneumonitis with small epithelioid tubercles or tiny foci of necrosis surrounded by dense capsules forming adjacent daughter lesions (3) a large focus of encapsulated pneumonitis with smaller nodose or conglomerate encapsulated foci extending for a considerable distance along lymphatic channels and (4) a cavity with adjacent tubercles and encapsulated necrotic foci Examination with special (PAS) stain was essential in demonstrating the organisms

Typically roentgenograms showed a circumscribed sharply outlined lesion within the lung fields Group 1 cases all showed this picture Some correlation might be expected between a softer outlined lesion and the cases in group 2 This was true in some instances but not in all In most cases there were only microscopic daughter lesions and they were probably too small to be evident on the film In group 3 cases roentgenographic densities were irregular and showed a soft nodularity In group 4 cases a nonspecific pneumonitis was first seen and later the cavity

Nine of the infections were originally diagnosed as probably tuberculosis No postoperative spread of the disease was noted

Histoplasmosis Three Fatal Cases with Disseminated Sarcoid like Lesions are reported by Henry Pinkerton and Lalla Iverson[6] (St Louis Univ)

Man 30 had progressive loss of appetite fatigue and fever Enlarged superficial lymph nodes were palpable and calcified abdominal node were visualized roentgenographically However no foci of infection could be found and results of specific tests (including blood cultures and agglutinations for paratyphoid and brucella organisms) remained negative Biopsy of an inguinal node showed discrete hard tubercle compatible with low grade miliary tuberculosi or sarcoidosis Guinea pig inoculation and cultures of the lymph

(6) A M A A b I t M d 90 456 467 Oct b 195

nodes yielded no organisms On roentgen examination no pulmonary changes were demonstrable and the only bony changes were in the metacarpals where slight demineralization was evident at the level of the epiphyses and in the carpals which also contained areas of decreased density He became increasingly anemic and the spleen *became palpable and tender He continued to lose weight steadily and* died eight months after onset

At autopsy gross lesions were found in lung thoracic and abdominal lymph nodes spleen and adrenals Microscopic examination revealed granulomatous inflammation in the lymph nodes lungs liver spleen kidneys and adrenals Organisms were found only in the adrenals and only periodic acid stain clearly demonstrated the presence of large aggregations of Histoplasma capsulatum in these organs

Until the time of their re evaluation the two other cases were similarly thought to be examples of sarcoidosis presumably because of the finding of numerous discrete epithelioid tubercles in excised lymph nodes or in the viscera removed at autopsy Schaumann bodies and asteroid bodies (common in sarcoidosis but not diagnostic of that entity) negative tuberculin skin reactions in the presence of a histologic picture resembling sarcoid splenomegaly bone changes (Case 1) and reversed albumin globulin ratio (Case 3) Although sarcoidosis and histoplasmosis may conceivably coexist it is more likely that the lesions represented histoplasmosis in tissue with effective immunity

Sarcoidosis and sarcoid lesions must be differentiated Even extensive replacement of lymphoid tissue by epithelioid tubercle is not an adequate basis for a diagnosis of sarcoidosis unless the accompanying clinical picture is characteristic and subsequent histologic studies show little variation from the usual morphologic pattern When the initiating organism is small or lacks a readily stained capsule as in tuberculosis or histoplasmosis it cannot be easily demonstrated in non necrotizing *epithelioid lesions Consequently extensive* search of areas of epithelioid reaction naturally fails to reveal organisms Even when the clinicopathologic features are more in keeping with sarcoidosis it is not unlikely that the histologic lesions thought to be characteristic may represent only a particular pattern of immunologic response

[The association of histoplasmosis with clinical and pathologic manifestations is characteristic of sarcoidosis as the authors point out has been previously observed The addition of these three cases suggests that the association is not a coincidence of two separate diseases but that H capsulatum is one of the possibly numerous causes of sarcoidosis —Ed]

TUBERCULOSIS

Developments in tuberculosis in recent years especially the advances in the medical and surgical treatment have stimulated increased general interest in this disease which for nearly half a century had become increasingly isolated from the field of internal medicine Despite this relative isolation in academic as well as practical medicine of the subject of tuberculosis the activity in thi field was always well represented in the YEAR BOOK under the previous distinguished editor of this section No apology is necessary for continuing a relatively heavy representation of the literature on this subject but an explanation and affirmation of edi torial policy in thi connection is believed warranted by the changing status of phthisiology

The relative medical isolation of the field of tuberculosis especially pulmonary tuberculosis was a consequence of the anatorium movement and the lack of any specific pharmaceutical rem dies for the di ea e Treatment of pulmonary tuberculosis thereby became for a time the responsibility exclusively of the phthisiologists who practiced principally in the sanatoriums and health resorts Before the advent of effective antimicrobial therapy surgery had already contributed importantly to the management of the disease and had initiated a return of some tuber culosis patients to the general hospitals for a part of their treatment Simultaneously the sanatoriums became increasingly transformed into hospitals for tuberculosis so that the most up to-date special hospitals for thi disease are equipped for more complicated diagnost c and treat ment p ocedures and can function virtually as general ho pitals Since such elaborate facilities are not everywhere available it follows that the general hospitals even now and increasingly as the disease comes under control must be prepared to accept tuberculosis patients if they are to d scharge their obligations and fully meet the needs of the r com munities There are indications not only that this trend with respect to institutional care is already advanced where hospital boards and profes sional staffs recogn ze the responsibility but also that home treatment may properly play an increasing part The editor bel eves that the in ternists and general practitioners will of necessity perform a greater part of the service to tuber ulosis patients in the future that they themselves recognize the need for their participation and that they are as much interested in th s disease as in any other

Since tuberculosis is a general systemic disease with pulmonary localization as the most frequent and conspicuou but rarely as the exclus ve manifestation the inclusion in this section of some articles on extrapulmonary tube culosis when the e have bearing on the general problem seems des rable even though other articles on these subjects may appear elsewhere in the volume —Ed

Effect of Corticotrophin (ACTH) Dihydrostreptomycin and Corticotrophin Dihydrostreptomycin on Experimental Bovine Tuberculosis in Rabbit Cortisone given to mice rats guinea pigs and rabbits infected with tubercle bacilli has a deleterious effect since treated animals have more extensive disease than controls and patients receiving cortisone for rheu

culosis in guinea pigs and rats although it is more deleterious than cortisone in ocular tuberculosis in rabbits

James M Bacos and David T Smith[7] (Duke Univ) studied the effects of ACTH and dihydrostreptomycin on pulmonary tuberculosis in previously sensitized and presumably partially immunized rabbits Rabbits were sensitized to tuberculin by subcutaneous injection of living avirulent tubercle bacilli and after 30-40 days allowed for sensitivity to develop were infected intratracheally with 0 25 ml suspension of bovine tubercle bacillus The rabbits were divided in three groups of about 20 each In each group some rabbits served as controls ome received dihydrostreptomycin some ACTH and some a combination of the two Experiments were terminated after 6 80 and 120 days respectively

All 12 untreated controls developed extensive progressive tuberculosis (Fig 26) Ten rabbits were given dihydrostrep tomycin 60 mg daily for 20 days then 30 mg daily Four developed progressive disease but less extensive than in the controls (Fig 27) Ten animals received ACTH with an initial dose of 2 5 mg every 6 hours then at successive 10 day periods reduction to 2 5 mg every 12 hours and 2 5 mg every 24 hours until the 30th day when 1 25 mg every 24 hours was given for the remainder of the experiment Pro ressive disease developed but the lesions were smaller than those of the untreated animals (Fig 28) Of 11 rabbits given both corticotrophin and dihydrostreptomycin in the doses used in the first two experiments 2 were killed the 4th day at the end of the experiment 2 had small scarred areas in the lungs (Fig 29) and 7 had normal lungs

These experiments indicate that corticotrophin does not materially reduce resistance of previously sensitized rabbits to tuberculosis and that it can be administered safely if dihydrostreptomycin is given simultaneously

[Th effects of corticotrophin and cortisone on tuberculous infection have been assumed by many to be identical and in most respects dele terious This study in the rabbit confirms the findings of LeMaistre and Tomps tt (Am Rev Tuberc 64 295 September 1951 J Exper Med 95 393 April 1952) in the guinea pig and in the rat that in experimental tuberculos s corticotroph n does not always have the same deleterious effect as cortisone Whether these d fferences apply also to the effects of the adm n t ation of these substances in tuberculosis in human beings is not determined but the results sugge t that there may yet be a useful

(7) Am R T be 67 201 211 F bru y 1953

application of ACTH in human tuberculosis especially in combination with antimicrobial therapy —Ed]

Electrophoretic and Chemical Serum Protein Fractions in Pulmonary Tuberculosis Bruno W Volk Abraham Saifer Linden E Johnson and Irwin Oreskes[8] (Jewish Sanitarium and Hosp Brooklyn) applied previously published quantitative photometric microprocedures for serum gamma globulin to the study of protein changes in approximately 100 cases of pulmonary tuberculosis of varying degrees of severity Periodic studies were also performed in 15 selected cases during one year to enable comparison of laboratory data with the clinical course of the disease The quantitative protein flocculation methods were compared in approximately 50 cases with chemical salt fractionation and electrophoretic procedures

All patients with active pulmonary tuberculosis including those with minimal lesions showed elevated gamma globulin levels The increase together with results of other procedures is believed to have diagnostic significance in the detection of early pulmonary tuberculosis and in evaluating arrested cases Gamma globulins increase (and the chemical and electrophoretic albumin globulin ratios decrease) significantly with the severity of the disease and tend to return to normal limits with the arrest of tuberculosis The estimates are therefore of prognostic value in patients with pulmonary tuberculosis Alpha and beta globulins which remain elevated even in arrested cases are not suitable prognostic indicators

These studies elaborated the evaluation of a new entity the ratio of total serum flocculation value to gamma globulin flocculation value for both normal subjects and diseased patients Total serum flocculation values correspond electrophoretically to the gamma globulin fraction plus a beta or beta lipoprotein fraction The gamma globulin flocculation values correspond to the electrophoretic gamma globulin values This ratio increases appreciably whenever beta globulin (or beta lipoproteins) increases e g in nephrosis and decreases whenever gamma globulins increase e g in multiple myeloma and liver diseases In tuberculous patients studied serially this ratio greatly decreased as the severity of the disease increased conversely in patients who improved decreasing gamma globulin and increasing total serum globulin ratio values were noted in serial observations

(8) Am Rev Tuberc 67 99 321 March 1953

Massive Hemoptysis from Arteriobronchial Fistula in Pulmonary Tuberculosis M Berard and Jaubert de Beaujeu[9] report two cases in which an arteriobronchial fistula was discovered during operation on tuberculous patients In the first the fistula was between the artery and bronchus to the right upper lobe in the second the main trunk of the pulmonary artery communicated with the left stem bronchus The two patients had violent profuse and repeated hemoptyses of such gravity that pulmonary resection was indicated Both were radiologically and clinically well at the time of the hemorrhages In both cases bronchoscopic examination was not informative but the nature of the hemorrhages was typical They were notable for their sudden onset violence and volume They appeared without warning and without premonitory fits of coughing The blood was not frothy and the hemorrhages stopped as abruptly as they began without that tailing off classically seen in bleeding from polyps and bronchial adenoma All these features suggest hemoptysis of bronchial origin rather than bleeding from the parenchyma of the lung

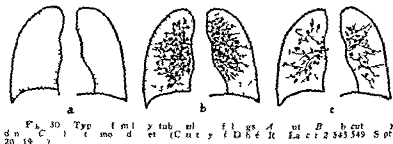
A review of the operative findings in nearly 100 resections for tuberculous stenosis revealed intimate cohesion between pulmonary artery and either stem or lobar bronchus in 12 cases In one case a hilar node between artery and bronchus had eroded into the walls of both structures so that they could not be separated without being torn It can thus be seen how caseous breakdown in a node or suppuration during an intercurrent infection might cause a fistula to form

Diagnosis of arteriobronchial fistula should always be considered in the presence of sudden massive hemoptysis in tuberculous patients with no radiologic evidence of a lesion to explain the bleeding

Miliary Tuberculosis in Children is discussed by Robert Debré[1] (Univ of Paris) and data are presented on 170 (101 girls) Sixty one were under age 3 and 22 were less than age 1 In nearly all miliary dissemination appeared almost simultaneously with primary tuberculosis Only eight had a history of tuberculosis one to six years earlier (conversion of skin test reaction or bone tuberculosis) In nearly half the cases meningitis was present on admission In about a fourth the

(9) Thor 7 15 155 J 1952
(1) Lancet 2 545 549 Sept 20 1952

history related mainly to meningitis and miliary tuberculosis was discovered only on routine x ray study of the chest and examination of the optic fundi in the others miliary tuberculosis was diagnosed first the history being that of a systemic disease with pyrexia fatigue anorexia and weight loss Temperature was usually high (102 104 F) but sometimes moderate (100 101 F) A normal temperature was never seen The pyrexia had lasted many weeks sometimes several months before the correct diagnosis was made Only a few patients had severe dyspnea with cyanosis Physical examination showed few signs The spleen was enlarged in about half the



F g 30 Typ f m l y tub ul f l gs A ut B b cut y d n C l t mo d et (C u t y f D b é R La c t 2 345 549 S pt 20 19)

cases In many no meningeal signs were found even though meningitis was demonstrable by lumbar puncture

Usually a positive tuberculin reaction gives the first clue but a negative reaction does not exclude a diagnosis of acute tuberculosis Technically correct x ray films are essential In the acute form the *granulie d Empis* (Fig 30 A) there are innumerable tiny spots in the lungs so small that there is no apparent difference in their size and so numerous that no part of the lung appears clear In the less acute types the spots are larger and unequal (*B* and *C*) They do not stipple both lungs so uniformly as in the first type and appear denser near the hilus and scarcer at the periphery In these subacute forms the spots vary from very dense to more discrete types (*granulie curable*)

The early tubercle of the choroid looks like a pink or yellowish clear spot with hazy edges on the red fundus sometimes brilliantly white in the center It is no larger than a fourth of the optic disk There can be many such lesions in both eyes— miliary tuberculosis of the choroid (Fig 31) In some cases larger tubercles are found and then there are only

one or two They have a white center and a yellowish corona and are surrounded by edematous tissue Typical acute miliary tuberculos s was associated with tubercles of the choroid in 55 of 61 cases the tube cles usually being of the miliary type Choroid tubercles were pre ent in only 18 of 40 subacute cases of the very dense type and in 40 of 69 of the more discrete type

Meningitis developed in 52 of the 61 children with the typical acute form and in only 58 of the 109 with the subacute form Eighty patients had meningitis on admission and in 28



F g 31 –T ł 1 f b 1 (Co t f D b R L t 2 545 549 Sep 9 195)

it was discovered during or after treatment mostly in the first months Therefore once treatment was started lumbar punc tures were repeated if not routinely at least for slight symp toms such as headache a new temperature rise or weight loss especially in the first two months In a few cases tubercle bacilli were grown on culture of cerebrospinal fluid that otherwise appeared normal but on repeated tap showed typical cell and protein changes

In the absence of meningitis the clinical course of strep tomycin treated miliary tuberculosis is usually simple Dysp nea generally subsides quickly Temperature begins to fall

soon but does not become normal until the second to fourth month of treatment The patient usually starts gaining weight only after the temperature begins to drop The erythrocyte sedimentation rate slowly returns to normal At the same time the lesions in the lungs and eyes clear remarkably Usually within a month there is dramatic improvement in the chest x rays The acute *granulie* may have almost disappeared leaving only a thin reticulum The larger spots become smaller and resemble those of the more acute form for awhile Clearing is either complete usually taking at least three months and sometimes nine though it may occur sooner or a thin network pattern may be left which appears unchanged in subsequent x rays Some of the tubercles of the choroid disappear completely on



Fig 3 —Emphy m t u b ll of lung due t m l y t be cul s (C t y of D b R L t 545 549 S pt 20 195)

the larger ones a black pigment can be seen and they leave a small scar that can be readily recognized

Of the 170 patients 9 died of acute miliary tuberculosis (and not of meningitis) in 3 of these rupture of emphysematous alveoli (Fig 32) was a major factor Tuberculosis of bones joints or lymph nodes was seen with the subacute form In two cases cerebellar tuberculomas were found and successfully removed Complications after completion of therapy were unusual Meningitis appeared in six patients with previously normal cerebrospinal fluid but these had had short courses of therapy Relapse was seen only twice The only other complications occurring after therapy were bone tuberculosis cervical adenitis and a discrete apical lesion one case each

For treatment Debre gives 0 02 0 04 Gm streptomycin/kg daily within the limits of 1 5 Gm for older children and 0 5 Gm for young ones The drug is given for at least eight

months in three injections daily para aminosalicylic acid 0 3-0 5 Gm/kg daily is given for the same period Treatment is continued longer if signs and symptoms regress slowly and is resumed (1) in case of relapse (2) if there is a secondary focus or (3) if meningitis develops In the event of meningitis 20-40 mg streptomycin is given immediately by the intrathecal route usually lumbar twice a day for a few days (in addition to two intramuscular injections a day) and then once a day until the cerebrospinal fluid is normal for at least two months after the intrathecal therapy

[The introduction of isoniazid was too recent at the time of publication of this paper to permit evaluation of the addition of this drug to the therapy of miliary and meningeal tuberculosis Improved results have been observed and American authorities are now agreed that when isoniazid is added to the standard streptomycin and PAS regimen the administration of streptomyc n intrathecally i rarely nece sary and should no longer be employed routinely in the therapy of meningitis This is an important advance because of th high incidence of deafness resulting from intensive intrathecal admin stration of streptomycin —Ed]

Intermittent Viomycin Therapy in Pulmonary Tuberculosis Employed Singly and in Combination with Intermittent Streptomycin or Daily Para Aminosalicylic Acid Forrest W Pitts Edward T O Dell Martin J Fitzpatrick William E Dye Frederic J Hughes Jr and Carl W Tempel (Fitzsimons Army Hosp) report on 80 patients treated with 2 Gm viomycin intramuscularly every third day 22 also received 1 Gm streptomycin intramuscularly on the days that they took viomycin 22 received 12 Gm PAS by mouth daily and the other 36 received no additional therapy Duration of therapy in all but one patient was 120 days The disease was moderately or far advanced and no patient had had previous chemotherapy for tuberculosis All patients were men 87% were white and ages ranged from 19 to 58 (average 31) The disease was generally severe with a high proportion of far advanced bilateral and cavitary tuberculosis The distribution of the clinical pathologic type of disease determined largely by serial x rays was similar in all three groups

Clinical response in nearly all patients on the three regimens was satisfactory only a few patients became clinically worse Response to viomycin alone was favorable within six to eight weeks in a patient with moderately severe laryngeal tuberculosis There was roentgen evidence of improvement in

(2) D Che t 23 241 245 M h 1953

77 95% of all groups and of moderate worsening in only 0 9% with viomycin alone only 9% showed moderate to appreciable improvement as against 39% with viomycin and streptomycin and 19% with viomycin and PAS combined Apparent cavity closure occurred in only 1 of 18 patients treated with viomycin alone in 6 of 28 patients treated with viomycin and streptomycin and in 1 of 14 patients treated with viomycin and PAS

Sputa had been positive by culture in all patients before therapy was started In 8 (36%) patients receiving viomycin alone 17 (47%) receiving viomycin and streptomycin and 10 (48%) receiving viomycin and PAS combined sputa were negative by culture at the end of treatment Viomycin resistance was not encountered before nor after therapy with combined regimens With viomycin alone 7% of those yielding positive cultures or 4 5% of the entire group showed organisms resistant (by the criteria set up) to viomycin after 120 days of therapy One of the 36 patients treated with viomycin and streptomycin yielded organisms which were completely resistant to 10 μg streptomycin/ml two months after completion of drug treatment the same patient yielded cultures completely sensitive to streptomycin

Nausea and vomiting in two patients was distinctly related to PAS by mouth daily all other manifestations of toxicity were attributed in whole or in part to viomycin Streptomycin or PAS may sometimes have been responsible but the incidence and severity of toxicity did not vary among the three regimens Toxicity was notably related to one of the two lots used and may therefore have been due in part to impurities rather than to the viomycin itself Clinical toxicity although common was usually transitory and minor and only once did it necessitate discontinuance of the drug Toxicity was manifested mainly by pain at the site of injection fever (usually mild) rash and malaise vertigo appeared in eight patients tinnitus in five hearing impairment in none

Results of one or more laboratory tests were abnormal in all patients during drug therapy Albuminuria occurred in 73% and cylindruria in 81% however albuminuria was noted in more than 6 of 10 specimens in only 4% of the patients Renal function as measured by Fishberg concentration and 15 minute phenolsulfonphthalein tests remained intact but 8%

of patients manifested significant decrease in urea clearance for at least two months after completing therapy. There were no disturbances in hemoglobin content, red or total white blood cell count. A high incidence of eosinophilia (5.38% total white cell count) was noted. This could not be correlated with the lot of viomycin or with clinical allergic phenomena. Results of liver function studies remained normal in all patients. Audiograms and caloric vestibular tests revealed no evidence of damage to the 8th cranial nerve. Appropriate studies showed no major electrolyte disturbances.

In striking contrast to the serious 8th cranial nerve dysfunction and serum electrolyte disturbance reported by others using viomycin daily, intermittent medication produced only minor toxic manifestations. However, pre-existing renal disease should probably remain a relative contraindication to viomycin therapy.

[Viomycin is the latest of the antituberculosis drugs to be approved for general use, although its clinical evaluation was begun several years earlier than that of the more prominent isonicotinic acid hydrazides. It is a drug of lesser value than isoniazid or streptomycin but of sufficient therapeutic effect, especially when used in combination with others, to be a useful addition to the growing list of antimicrobial agents for the treatment of tuberculosis.—Ed.]

↓ The following abstracts relating to isoniazid represent only a small segment of the literature which has appeared in the past year concerning the treatment of tuberculosis with this agent. Because it is impossible to include a full representation of this subject and because many important observations relating to the clinical use of isoniazid have not yet appeared in print, it seems appropriate here briefly to summarize the progress which has been made in the evaluation of this much discussed drug.

It is now apparent that the dramatic symptomatic improvement observed in the early clinical studies of the hydrazine derivatives of isonicotinic acid [illegible] to be seen more frequently with iproniazid than with isoniazid. [illegible] many times more toxic, however, than isoniazid. In evaluation of the therapeutic effectiveness of the two drugs there have been few indications that iproniazid is superior with respect to such objective criteria as rapidity and extent of roentgenologic improvement or elimination of tubercle bacillary output in the sputum. Whatever therapeutic advantage there may be in favor of iproniazid is outweighed by its greater toxicity. Because of this iproniazid has not been made available for general [illegible] isoniazid has been freely available for prescription [illegible] during the past year. Many thousands of patients have thus been treated with this [illegible] and the early impression concerning its relatively low toxicity [illegible] been confirmed. As with most other potent antimicrobial agents, however, [illegible] is not free of toxicity. Most of the untoward reactions [illegible] of minor importance, but occasional serious reactions are recorded [illegible] convulsions, psychotic manifestations, blood dyscrasias and hepatic damage.

With respect to the therapeutic effectiveness of isoniazid there is general agreement that it is a potent antimicrobial agent in tuberculosis

Its usefulness is recognized particularly in the treatment of miliary tuberculosis and tuberculous meningitis There is accumulating evidence that in the treatment of miliary tuberculosis isoniazid protects against *the development of meningitis more effectively than streptomycin* alone or combined with para aminosalicylic acid (PAS) In the treatment of tuberculous meningitis itself the addition of isoniazid to the usual streptomycin PAS regimen has strikingly reduced the mortality at least within the first five or six months of treatment for which there are data of statistical significance The important contribution which isoniazid can make to the therapy of tuberculous meningitis probably results from its free permeability into the cerebrospinal fluid It appears probable that intrathecal streptomycin therapy will rarely be necessary under com bined streptomycin and isoniazid therapy by other routes

Despite the demonstrated value of isoniazid in miliary and meningeal tuberculosis and the agreement that it is essential in the treatment of these forms its status in the treatment of pulmonary tuberculosis is not so well established Nor does it necessarily follow that because it is highly effective in generalized miliary disease and in meningitis it must be so in pulmonary tuberculosis also The conditions are different in pulmonary tuberculosis in which the pathologic factors of massive casea tion and excavation together with secondary fibrosis set different require ments for antimicrobial therapy The chronicity and partial irreversibility of the established disease require that any agent which is bacteriostatic rather than bactericidal (and such is true of virtually all antimicrobial agents in vivo) must continue to exert suppressive effects for a long time The factor of the rate of emergence of bacterial resistance is there fore of the greatest importance

It was found early in the clinical trials of isoniazid in pulmonary tuberculosis that resistant colonies could be demonstrated with relative ease even before treatment and that the proportion of resistant colonies increased appreciably in many patients after only a few weeks of treat ment It was therefore generally assumed that a rapid progression of such shifts in the bacterial population would in most instances lead to an early neutralization of drug activity Clinical experience however has not conformed entirely to these predictions and the preponderance of evidence is that the therapeutic effect of isoniazid administration is sus tained up to at least six months in many if not in most instances despite considerable shifts in the proportion of drug susceptible organisms More over the precise level of in vitro resistance which signifies loss of thera peutic activity has not been defined and appears to be less readily deter minable than is the case with streptomycin Fair correlations between in vitro results and clinicoroentgenologic observations have been reported in several publications but this is not uniformly the case

In the large co-operative study (see this YEAR BOOK p 205) con ducted by the United States Public Health Service of comparative regimens in the treatment of pulmonary tuberculosis isoniazid compares favorably in clinical and roentgenologic results up to 28 weeks (and longer according to observations not yet published) with a streptomycin PAS regimen and with a streptomycin isoniazid regimen With respect to the relative rates of reduction in the proportion of positive sputum cultures superiority was demonstrated for the streptomycin isoniazid regimen b th re was little difference between the other two Whether or not isoniazid is as good given alone as in combination or is as good as other combinations the evidence is impressive that it is at least as potent as any other single agent and that its action is sustained longer than

that of streptomycin which is the only other agent comparable to isoniazid in potency It is w ll establ hed that streptomycin becomes therapeutically ineffective relatively rapidly unless combined with some other agent When combined with PAS as has become standard practice an effective treatment can usually be sustained for many months but not indefinitely since bacterial resistance to both drugs usually develops eventually if pulmonary cavities persist

The questions of whether isoniazid is best used by simply adding it to the streptomycin PAS combination by combining it with one or the other of them by administering it independently or by holding it in reserve against possible failure of the streptomycin PAS regimen are as yet unanswered The conflicting pronouncements which have been offered in favor of one or the other policy have added little but confusion It appears probable that the chemotherapy of choice in tuberculosis will be a matter of individualization rather than of the indi criminate application of a single regimen to all clinical types and varieties of the disea e—Ed

Action of Isoniazid (Isonicotinic Acid Hydrazide) on Intra cellular Tubercle Bacilli G B Mackaness and N Smith[3] (Oxford England) found that in conventional cultures in Dubos Davis medium H37Rv (human) and Branch (bovine) strains of Mycobacterium tuberculosis were inhibited respectively by isoniazid concentrations of 0 06 and 0 03 μg /ml for 14 days After this time the behavior of the two strains was consistently different After prolonged incubation growth appeared in H37Rv cultures in concentration of isoniazid ranging at least as high as 1 0 μg /ml but no viable culture could be recovered from the original Branch inoculum

Macrophage populations were prepared which contained more than 70% of tubercle bacilli infected cells In the Branch macrophage cultures the morphologic change (occasional elongated forms some of which were excessively long) in the bacilli grown in the presence of 0 01 μg isoniazid/ml was indication that inhibition had been only partial Three cultures containing 1 0 0 1 and 0 01 μg isoniazid/ml were washed free from the drug and reincubated in isoniazid free medium After three days more the macrophage degenerated in the cultures which had previously contained 0 01 μg /ml The degeneration was due to the unrestrained growth of the tubercle bacillus comparable with that seen in infected control cultures of equivalent age Cultures which had received 0 1 and 1 0 μg /ml remained normal and healthy in appearance and no growth of bacilli could be detected In further titrations intra cellular bacilli of the Branch strain were completely inhibited for at least 11 days by a concentration of 0 05 μg isoniazid/ml

(3) Am R T b 66 125 133 A g t 195

An attenuated H37Rv strain was used as the fully virulent strain is so cytotoxic that it is not suitable for test organism This strain when growing as an intracellular parasite was also inhibited by isoniazid at a concentration of 0 05 μg/ml On the seventh day when most cells of the infected controls were crammed with proliferated bacilli there was still no evidence of growth of bacilli in the presence of 0 05 μg/ml At this time two cultures containing respectively 0 1 and 0 05 μg isoniazid/ml were washed free from isoniazid and the macrophages were allowed to dry in contact with the cover slip They were then covered with a thin layer of oleic acid albumin agar medium sealed and reincubated Microcolonies of bacilli appeared among the remnants of almost every macro phage of both cultures after four to six days of incubation It is apparent that intracellular bacilli had survived for seven days in the presence of fully bacteriostatic concentrations of isoniazid similar to the behavior of conventional cultures

Isoniazid differs from most of the antituberculous drugs which have been tested by this method in that its activity is not significantly lowered by an intracellular location of the tubercle bacillus The drug seems to enter freely into cells and exert its full bacteriostatic action in this environment

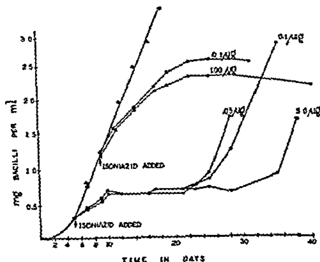
Mode of Action of Isoniazid was studied by W R Barclay R H Ebert and D Koch Weser[4] (Univ of Chicago)

METHOD —A series of six tubes containing Dubos liquid medium was inoculated with H37Rv a virulent strain of Mycobacterium tuberculosis On the fifth day drugs were added so as to result in 0 05 0 1 or 1 0 μg isoniazid/ml or 0 1 or 1 0 μg streptomycin/ml culture medium with one tube serving as control Drugs were added on the ninth day to six of seven tubes in a similar series resulting in concentrations of 0 1 10 0 or 100 0 mg isoniazid or 1 0 10 0 or 100 0 mg streptomycin/ml Growth was measured turbidom trically

Isoniazid did not immediately stop growth (Fig 33) The tubercle bacilli continued to multiply rapidly at first but then more and more slowly until the population had approxi mately doubled and then growth ceased This type of delayed bacteriostasis resembles that produced by the sulfonamides on organisms susceptible to these drugs The action of isoniazid was apparently the same for large as for small numbers of organisms in the medium and was the same if added in the arithmetic phase as when added in the logarithmic phase of

(4) Am. Re T ber 67 490 496 Ap 1 1953

growth Identical initial curves were obtained with massive concentrations (100 μg/ml) as with low concentrations (0 05 μg/ml) of drug Although 100 μg isoniazid/ml eventually arrested cell multiplication the cell mass remained constant when growth had ceased and apparently the bacteria did not disintegrate at least not immediately Lower concentrations of isoniazid were not capable of permanently arresting growth and in approximately two weeks cell multiplication began



F g 33—Eff ct f so d g wth f H37R (C rt y of Ba cl y W R f Am. R T b 67 490 496 Ap l 1953)

again These cells went through first a logarithmic and then an arithmetic phase of growth and in the arithmetic phase paralleled the original culture When tested for isoniazid susceptibility the cells were resistant to whatever concentration of drug was present in the medium in which they developed The effects of isoniazid were in contrast to those of streptomycin which in a concentration of 100 μg/ml almost immediately arrested growth In approximately three days the turbidity of the culture decreased presumably due to the lysis of dead cells and reflected the bactericidal action Resistant organisms eventually appeared however and growth in the culture began once more A small quantity 1 μg strepto

mycin/ml added to the culture on the ninth day lowers but does not arrest the rate of growth

Experiments with C^{14} labeled isoniazid showed that susceptible organisms do absorb and fix the drug to the cell substance whereas resistant organisms take up practically none of the compound This lends weight to the hypothesis that isoniazid actively participates in the metabolism of the cell thereby blocking the formation of a substance essential for cell division

Distribution and Excretion of Radioactive Isoniazid in Tuberculous Patients W R Barclay R H Ebert G V Le Roy R W Manthei and L J Roth[5] (Univ of Chicago) used isoniazid labeled with radioactive carbon to study the distribution and excretion of this agent in tuberculous patients Peak levels of drug were reached in blood and plasma within an hour of intramuscular injection Levels fell rapidly during the first eight hours but measurable quantities of drug were found in blood and plasma three to seven days after a single injection Isoniazid is freely diffusible and is found in appreciable amounts in uninfected tissues and cerebrospinal fluid of patients with tuberculosis The highest concentrations in normal tissue were found in lung and skin The drug is excreted chiefly by the kidneys with small amounts excreted in the feces and by the lungs as carbon dioxide

Isoniazid diffuses freely into dense caseous lesions in both lung and lymph nodes and is present in high concentration three to five hours after injection A drug with this property is ideally suited to tuberculosis therapy Isoniazid is found in pleural fluid in high concentration 2½ hours after injection and measurable quantities remain 3 days later

[The precise measurements of isoniazid in body fluids and tissues by this technic confirm and extend previous observations by chemical methods which indicated a high degree of diffusibility and a rapid excretion of the drug Of particular significance are the high concentrations obtainable in cerebrospinal fluid in pleural fluid and in dense caseous lesions In these respects as well as in its ability to maintain full bacteriostatic action on intracellular tubercle bacilli (see Mackaness and Smith this YEAR BOOK p 193 isoniazid possesses theoretical advantages over streptomycin which appear for the most part to be also confirmed in practice —Ed]

Isoniazid (Isonicotinic Acid Hydrazine) in Treatment of Miliary and Meningeal Tuberculosis Charles M Clark (U S P H S) DuMont F Elmendorf Jr William U Cawthon

(5) J A M A 151 1384 1385 Ap 18 1953

Carl Muschenheim and Walsh McDermott[6] (New York Hosp Cornell Med Center) report observations on 20 patients treated only with isoniazid during the period of study A few had previously received various other forms of antituberculosis therapy Diagnosis of miliary tuberculosis was based on pres ence of the triad acute febrile illness characteristic dissem inated densities in chest x rays and demonstration of acid fast bacilli on microscopic examination of body discharges or of Mycobacterium tuberculosis by culture Diagnosis of men ingeal tuberculosis was established by culturing Myco tuber culosis from the cerebrospinal fluid or by demonstration of cerebrospinal fluid findings of nonpurulent meningitis with a low concentration of sugar (less than 35 mg /100 ml) in a patient with a bacteriologically proved lesion of tuberculosis elsewhere The 20 patients included 10 with uncomplicated miliary tuberculosis 4 with miliary tuberculosis complicated by meningitis and 6 with meningitis alone Daily dosage of isoniazid was 10 mg /kg throughout the first week of admin istration then 7 5 mg /kg regardless of the course

Of the 14 patients with miliary tuberculosis 12 had remis sions duration of treatment being 3 7½ months Two died both of meningitis during the first week of therapy No evidence of meningitis appeared in those free from this com plication when isoniazid therapy was started Complete defer vescence occurred in 7 49 days

X ray studies showed an impressive degree of clearing of disseminated densities in all 12 patients The shortest period of therapy in which definite roentgen improvement occurred was 14 days and the longest period without favorable change was 88 days In all of five patients who received isoniazid for 130 days the densities completely disappeared In some in stances there was an associated pneumonic component the densities disappeared completely whereas the pneumonic com ponent persisted although it was regressing There was a correlation between reversal of infectiousness as demonstrated by smear and culture and roentgen change

These results were compared with those obtained with 3 Gm streptomycin daily in 1946 Figure 34 shows average tem perature values for the first seven weeks of treatment in two groups of patients (eight each) without complicating menin

(6) Am. R T b 66 391 415 O t b 1952

mycin/ml added to the culture on the ninth day lowers but does not arrest the rate of growth

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(5) J A M A 151 1384 1388 Ap 18 1953

Of the four patients with miliary tuberculosis and meningitis two died within the first week of therapy and one improved dramatically In the fourth with only bacteriologic evidence of tuberculous meningitis cerebrospinal fluid cultures became negative and clinical signs of meningitis did not develop

Of the six patients with tuberculous meningitis without miliary tuberculosis one died during the first week of therapy The other five had been previously treated with streptomycin Two of these had been deteriorating steadily one remained comatose despite isoniazid therapy although cerebrospinal fluid findings improved but the other showed striking clinical improvement after 21 days of therapy The asymptomatic course of the three other patients who had only abnormal cerebrospinal fluids at the start of isoniazid therapy remained unaltered but in every instance cerebrospinal fluid abnormalities gradually receded and with one exception normal values for the various components were all present by the 22d week of therapy

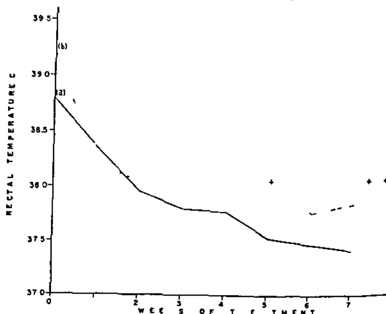
Comparison of the uniformly satisfactory results in the isoniazid treated patients with uncomplicated miliary tuberculosis with results previously obtained with streptomycin permits the inference that the antituberculous activity of isoniazid in man is equivalent and probably slightly superior to that of streptomycin However no conclusion can be made as to the effectiveness of the drug in pulmonary tuberculosis in which the situation is complicated by unhealed lesions and necrotic lung

[It is of interest that in the nine months that have elapsed since the publication of this paper none of these patients treated with isoniazid alone has relapsed It is particularly significant that none of the patients with miliary tuberculosis who did not have meningitis before the start of treatment has developed this complication This advantage of isoniazid has been reported in unpublished communications by numerous other observers Indeed there is yet to be reported a single instance of a patient with miliary tuberculosis developing meningitis while receiving isoniazid therapy Such an occurrence in contrast was common with streptomycin alone and was not rare even under combined streptomycin and PAS therapy (see Debre this YEAR BOOK p 185) —Ed]

Treatment of Pulmonary Tuberculosis with Hydrazide Derivatives of Isonicotinic Acid Irving J Selikoff Edward H Robitzek and George G Ornstein[7] (Sea View Hosp Staten Island N Y) report on 175 patients with active pulmonary

(7) J A M A 150 973 980 N 8 1952

gitis There were no significant differences in the speed with which complete defervescence occurred nor in the extremes of the shortest and longest periods of therapy required for attainment of the afebrile state For comparison of roentgen changes streptomycin treated patients with miliary tuberculosis with or without meningitis were included In seven of the eight streptomycin treated patients impressive roentgen



F g 34—T mp t r s s of ght p t ent w th ınt lly u c mpl c ted m l ry t b rc l s t ted w th so d al (s l d l) and f g t m l pat ts t ted w th at ept my l (b k n l) ka h p t pl tt d ep s nts e ge f 56 al e w kly g of da ly h gh t mp at f r th e ght pat ts ın h g o p *A* nd c t p t e tm t av g f 6 t mp at e only d *B* p et atm t a g f 36 t mp rat s only O set f t be lou men g t n t pt myc n t at d p p o ly n 35th 52d d 54th day f t t me t ınd cated by (C te y f Cla k C M *t al* Am Re T b 66 391 415 O t be 195)

clearing occurred by the 99th day and in six the densities disappeared by the 157th day of therapy These values are essentially the same as the 88 and 130 days in the isoniazid treated series All the streptomycin treated patients were excreting tubercle bacilli when therapy was started four months later Myco bacterium could be isolated from only three This compared with two of nine for the corresponding interval in the isoniazid treated series

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(7) J A M A 150 973 9 0 N v 8 1952

tuberculosis many of whom also had other forms of tuberculosis Each patient was considered unlikely to benefit from known standard methods of therapy and almost all represented a failure of such therapy Iproniazid was given to 101 patients for three to seven months and isoniazid to 65 patients for two to five months Nine patients not previously treated with streptomycin were given streptomycin and a hydrazine derivative for three months The dose of iproniazid was standardized at 4 mg /kg daily significantly lower doses were ineffective and higher ones excessively toxic The isoniazid dosage 4-8 mg / kg was effective but not necessarily optimal The drugs were given in three divided doses

In febrile cases defervescence was usually attained within three weeks (average 8 10 days) Defervescence was accompanied by an equally rapid reversal of systemic toxicity even in almost moribund patients The reversal was a unique effect of hydrazide therapy and occurred with a regularity and to a degree not observed with hitherto utilized antimicrobial agents Weight gain accompanied return of appetite Beneficial roentgen changes (closure or significant reduction of cavity and clearing of exudate) were seen in 60 3% of the patients Some patients responded favorably within two to three months However such favorable roentgen changes in significant numbers were only apparent in the beginning of the sixth month A deleterious effect (reopening of a cavity appearance of a new cavity or enlarging of old or appearance of new exudate) occurred sometimes

A rapid and significant reduction in cough and expectoration was achieved This effect appeared simultaneously with systemic improvement and persisted Conversion of sputum occurred in about 25% of cases Therapeutic effect was also noted in a wide variety of extrapulmonary lesions including those of the larynx tongue gastrointestinal tract bone bladder lymph nodes pleura skin and tuberculous sinus tracts and wounds

When there were toxic side effects they were principally in the central nervous system and to a lesser extent in the autonomic nervous system Symptoms included hyper reflexia headache involuntary muscle twitching peripheral neuropathy mild euphoria and excitability constipation vertigo difficulty in initiating micturition oral dryness minor difficulty in

visual accommodation and variations in sexual stimulation and activity These symptoms commoner with iproniazid occurred at therapeutic dosage levels of 4 mg/kg At this level however *they did not contraindicate* therapy but with higher dosages they became more severe and *with doses of 15 mg/kg* hazardous With isoniazid side effects in *the nervous system* were much less severe but still occurred Although they were sometimes noted with doses of 4 and 8 mg/kg and necessitated *reducing* the dosage *this* was uncommon Laboratory evidence of toxicity was rare or absent Side effects were commoner in elderly persons in patients with unstable personalities convulsive tendencies or a history of psychosis and in the presence of anemia Prostigmin* bromide was effective in alleviating several of the side effects Adrenergic drugs and *surgical anesthesia may aggravate iproniazid side effects*

The exact place of hydrazide therapy *in the total program* of tuberculosis therapy cannot yet be determined Results in the nine patients treated with streptomycin and the hydrazide derivatives combined gave promise of enhanced superiority *over treatment with each independently*

Isoniazid and Its Isopropyl Derivative in the Therapy of Tuberculosis in Humans Comparative Therapeutic and Toxicologic Properties Edward H Robitzek Irving J Selikoff Erich Mamlok and Anna Tendlau* (Sea View Hosp Staten Island N Y) compared 101 patients receiving 4 mg iproniazid/kg 65 receiving 4 and 8 mg isoniazid and nine receiving *combined streptomycin and iproniazid or isoniazid therapy* for two to seven months Dose for dose iproniazid controlled the systemic effects of tuberculosis more promptly and completely than isoniazid X ray and sputum changes showed approximately equal benefit Drug toxicity was encountered more often and more intensely with iproniazid than with isoniazid Beneficial effects *with each drug* were *seen in the treatment of various extrapulmonary entities*

The combination of streptomycin with either isoniazid or iproniazid appeared to demonstrate some superiority to either drug alone on the basis of a short term study of nine cases Clinical resistance to hydrazide therapy was not impressive With one exception the first 17 patients under treatment *for* 42 277 days continued to show in vitro sensitivity

* Dis Ch 27 2 15 J ary 1955

Optimal dosage and regimen for isoniazid were not determined but were believed to exceed 8 mg/kg/day in divided doses

[These differences between isoniazid and iproniazid explain some of *the confusions and the conflicting early reports* regarding *the clinical* effects of hydrazide therapy The more dramatic symptomatic responses to iproniazid were of course not observed by those using only isoniazid who were then inclined to underrate isoniazid until the slower but more important objective changes became manifest —Ed]

Treatment of Pulmonary Tuberculosis with Isoniazid Interim Report to Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee [9] In a clinical trial 331 patients with various forms of pulmonary tuberculosis

COMPARISON OF RESULTS WITH STREPTOMYCIN PAS AND ISONIAZID

	STREP PAS	ISONIAZID
General condition		
Improvement 2+	22	32
Improvement 1+	52	50
No change	22	15
Deterioration	2	3
Death	2	1
Weight gain		
14 lb or more	14	36
7 13 lb	26	32
Less than 7 lb or no change	46	23
Weight loss	13	8
Radiograph		
Improvement 2+ or 3+	29	26
Improvement 1+	37	29
No change	32	38
Deterioration	1	6
Sputum		
Pretreatment		
Direct positive	82	84
Positive culture only	18	16
Negative	0	0
At 2 mo		
Direct positive	49	54
Positive culture only	26	24
Negative	26	23

were studied 173 were treated with isoniazid (200 mg daily) and 158 with streptomycin (1 Gm daily) and PAS (20 Gm daily) Treatment was randomly allocated and at the time of selecting a patient the treatment he would receive was unknown to the physician Results at the end of three months treatment and other observations are summarized in the table

Three main groups of patients were observed group 1

(9) B M J 2 735 746 Oct 4 195

with acute rapidly progressive disease of recent origin group 2 with other forms suitable for chemotherapy group 3 with chronic disease considered unlikely to respond to chemotherapy On admission the two treatment series had a similar distribution of patients with severe and less severe illness

Isoniazid showed low toxicity at the dosage used and for the period of treatment At the end of three months the patients on isoniazid (H) showed more improvement in their general condition than the other patients (SP) but the differences were not great Average weight gains were considerably greater in the H group (11 lb) than in the SP group (6 lb) Temperature fell to normal in 67% of febrile SP patients and in 56% of febrile H patients In the acute group 1 temperature fell to normal in 64% of SP patients and 68% of H patients Of patients with a sedimentation rate over 20 before treatment 22% of the SP group and 20% of H group had a rate of 10 or less after treatment

Radiologic changes were independently assessed Two plus or 3 plus improvement was seen in 29% of SP and 26% of H patients in the acute group it was seen in 37% of SP and 40% of H patients There was radiologic deterioration in 1 SP patient and three deaths deterioration was seen in 10 H patients and there was *one* death Before the end of the second month 26% of the SP and 23% of the H patients had negative sputum

On the basis wholly of short term results it appears that isoniazid is an effective drug in pulmonary tuberculosis but when given alone it is not more effective than streptomycin plus PAS

Bacillary resistance to isoniazid was found in 11% of patients at the end of the first month in 52% at the end of the second and in 71% at the end of the third Lack of progress as assessed by radiologic change was found to be related to emergence of drug resistance This is therefore a most serious problem affecting the use of isoniazid

Isoniazid in Treatment of Pulmonary Tuberculosis Second Report to Medical Research Council by Tuberculosis Chemotherapy Trials Committee [1] Study material included 364 patients from 40 hospitals 142 were treated with 1 Gm streptomycin daily and 100 mg isoniazid twice daily (SH) 102

(1) B M J 1 521 536 M 7 1953

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(1) B t M J 1 5 1536 M 7 1953

with 1 Gm streptomycin daily and 5 Gm sodium PAS four times daily (SP) and 120 with only 100 mg isoniazid twice a day (H) Three main disease groups were observed (1) acute rapidly progressive disease of recent origin (2) other forms suitable for chemotherapy and (3) chronic disease unlikely to respond to chemotherapy The distribution of patients in the three treatment series at admission was similar with respect to severity of illness

At the end of three months the general condition of most patients improved There was little difference in the three series Average weight gains were 13 lb for the SH 6 lb for the SP and 15 lb for the H series Two plus or 3 plus roentgen improvement was seen in 38% of the SH 31% of the SP and 23% of the H cases There was little difference over the whole range of response between patients on SH and SP but these patients responded better than those on H There were roentgen deterioration in 3 cases and death in 1 with SH deterioration in 1 and deaths in 2 with SP and deterioration in 11 and death in 1 with H At three months sputa were negative on smear and culture in 67% of the SH 55% of the SP and 37% of the H series Judged solely from results at three months combined streptomycin and isoniazid therapy was the most effective although its superiority over streptomycin and PAS was not great

Bacillary resistance to isoniazid in patients with positive cultures tested at three months was found in 62% of the H series and in only 13% of the SH series streptomycin resistance was found in 11% of the SH series at three months Thus the combination of streptomycin and isoniazid was equally effective in preventing streptomycin resistance and isoniazid resistance Moreover SH treatment was as effective as SP treatment in preventing streptomycin resistance Patients with organisms initially streptomycin resistant were apparently not protected from development of isoniazid resistance by SH treatment those with organisms initially PAS resistant (who had had prior treatment with PAS alone) were not protected from streptomycin resistance by SP treatment Thus none of the three drugs should be used by itself nor should two of them be used in combination for a patient with organisms already resistant to one of the pair

[It should be noted that in this British study of comparative regimens

the streptomycin PAS regimen consists of streptomycin 1 0 Gm *daily* and *PAS 20 Gm per day and the isoniazid regimen of 100 mg twice daily* The dosage of both streptomycin and PAS is considerably greater than that used in similar studies on this side of the Atlantic and the dosage of isoniazid is below the average employed here This second report of the Medical Research Council like the preceding first report covers only the first three months of treatment but includes additional regimens

As in the United States Public Health Service reports (this YEAR BOOK below and p 207) a slight superiority is demonstrated for strepto mycin isoniazid over streptomycin PAS and over isoniazid alone The apparent advantage however of streptomycin PAS over isoniazid alone is not confirmed in the American study which is perhaps accountable by the differences in dosage The impressive fact is that any differences in results either at three months as found here or at six months as found in the American study are not large with one exception The exception is in the proportion of sputum cultures becoming negative in which the streptomycin isoniazid regimen is distinctly superior to the other two —Ed]

Control Study of Comparative Efficacy of Isoniazid Streptomycin Isoniazid and Streptomycin Para Aminosalicylic Acid in Pulmonary Tuberculosis Therapy III Report on 28 Week Observations on 649 Patients with Streptomycin Susceptible Infections is presented by Frank W Mount and Shirley H Ferebee (U S P H S) Three regimens were under investi gation (1) 1 Gm streptomycin twice weekly plus 10 12 Gm PAS daily (203 patients) (2) 1 Gm streptomycin twice weekly plus 150 300 mg isoniazid daily (219 patients) and (3) 150 300 mg isoniazid daily (227 patients) Excluded from the report were 144 patients who had been elected for the program but whose chemotherapy deviated from the pre scribed one chiefly through departure from hospital More patients treated with streptomycin and PAS left the hospital and twice as many exhibited severe drug intolerance princi pally to PAS as in either group receiving isoniazid Clinical and roentgen response of patients up to the time of deviation resembled that of patients who remained in the hospital and no apparent bias resulted from their omission Despite the loss of patients the three groups appeared to have a similar distribution of severe disease and were comparable in age race and sex Most of the 649 patients (62%) had moderately or far advanced cavitary disease approximately half that number (33%) had advanced disease without cavity and a few (5%) had only minimal disease

Three patients in the streptomycin PAS group and two in the isoniazid group died of tuberculosis eight patients in

( ) Am R T b 67 539 543 Ap 1 1953

the streptomycin isoniazid group died four of tuberculosis three of myocardial infarction and one of cerebral hemorrhage

Evaluation of chest films is presented in the table With each succeeding interval the films of an increasing number of patients showed change from the pretreatment status After 16 weeks approximately three fourths of each group had either improved or grown worse After 28 weeks of therapy distribution among the three groups was remarkably similar Approximately 8% of each group showed some deterioration and 72 74% had improved The range between the three regimens was only slightly greater when improvement is restricted to the marked and moderate categories (47 54%)

Sputa were examined directly and cultured at four week intervals Tubercle bacilli were detected in 4 20% more of

PROPORTION OF EACH GROUP SHOWING MARKED OR MODERATE IMPROVEMENT

REGIMEN	WEEKS TREATMENT						
	4	8	12	16	20	24	28
Streptomyci PAS	3 9	13 1	2? 2	32 0	39 8	43 7	46 7
Streptomvcin Isoniazid	5 2	17 1	28 4	41 3	47 1	51 6	53 9
Ison az d	4 8	1 7	21 4	33 2	40 6	46 4	50 7

the specimens by culture than by direct examination The proportion of specimens in which tubercle bacilli were detected by each method decreased rapidly on all regimens during the early weeks of treatment By direct examination the incidence of positive sputa showed little change after 16 weeks of treatment on any regimen By culture there was a decrease in the proportion positive for tubercle bacilli among only the streptomycin isoniazid patients after 12 weeks The greatest reduction by either method was observed under streptomycin isoniazid treatment with little difference between the two other regimens

The three drug regimens appeared to be equally effective in reducing fever slightly less than 10% of the patients in each group remained febrile after 28 weeks The proportion of patients in each group at least 10% underweight was reduced after 28 weeks of treatment to approximately one third from approximately one-half at selection

Effect of Streptomycin on Emergence of Bacterial Resistance to Isoniazid United States Public Health Service Co operative Investigation[5] Preliminary data on bacterial susceptibility are reported for 150 patients all of whom were

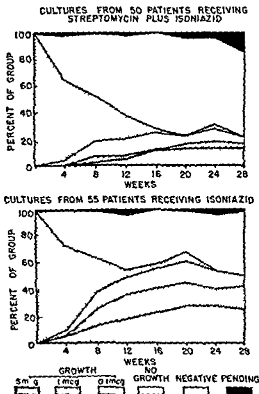


Fig 35 — Pes lt { cult am tions nd iso az d u pt b l ty te t (C rt y { U S P H S Am R Tu 6 5 3 56 M y 19 3)

treated for 28 weeks Isoniazid susceptibility was determined for cultures of tubercle bacilli from patients treated with isoniazid alone or combined with streptomycin and streptomycin susceptibility for organisms cultured from patients who received streptomycin in combination with isoniazid or PAS

Experience with isoniazid is limited Determination of the

(5) Am Rev T b 67 553 567 M y 1953

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Regimen	Weeks on treatment						
	4	8	12	16	20	24	28
Streptomycin PAS	3 9	13 1	22 2	32 0	39 8	43 7	46 7
Streptomycin Isoniazid	5	17 1	29 4	41 3	47 1	51 6	53 9
Isoniazid	4 8	12 7	21 4	33 2	40 6	46 4	50 7

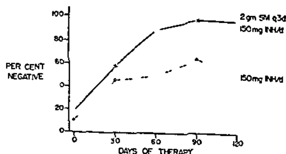
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to an analysis of the group of patients who continue to discharge tubercle bacilli disregarding the obvious significance of the size and characteristics of the group in which the cultures become negative Figures 35 and 36 show the emergence of resistance in the total treatment population All cultures positive for Mycobacterium tuberculosis obtained after 28 weeks of treatment contained tubercle bacilli which had lost some measure of their initial susceptibility to the particular drugs (excluding PAS) to which they had been exposed However in another respect the regimens were not equal tubercle bacilli were detected in the cultures of half of the isoniazid one third of the streptomycin PAS and one fourth of the streptomycin isoniazid patients

In managing tuberculous patients these regimens offer no easy choice for the clinician The regimen which offers the greatest probability of negative sputum also provides near certainty of bacilli resistant to both streptomycin and isoniazid if the sputum has not become free of tubercle bacilli The other two regimens which offer less chance of sputum conversion will on the other hand produce bacilli resistant to only one of the potent drugs leaving either streptomycin or isoniazid for subsequent use

Incidence of Bacterial Resistance Encountered with Tuberculosis Chemotherapy Regimens Employing Isoniazid Alone and in Combination with Intermittent Streptomycin Although evidence is insufficient to correlate loss of clinical response



P tag calcul ted t m f mb f p t t w th
k w lt al t t t m f l t on
F g 37 —Sp t m co d g b t l g l t n f a d d
so d t p nty g m P l m y p rt ba ed ly S pt 4 195
(Court y f Dy W E et l Am R T b 67 106 107 J y 1953)

point that represents a change in the character of the bacterial population significant in terms of drug neutralization must await correlation with clinical and roentgen data A few pre treatment cultures revealed growth of less than 50 colonies

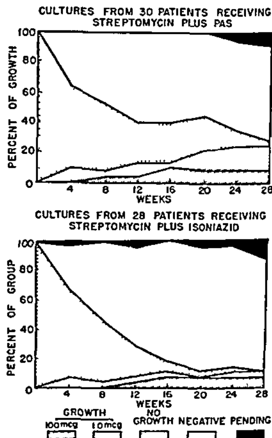


Fig 36—R lt f cult m t on d t ptomy sc jt b l ty t st (C rt y f U S P H S Am R T be 67 553 567 May 1953)

in 0 1 μg isoniazid/ml but none showed growth exceeding 50 colonies in 0 1 μg or any growth in higher concentrations Accordingly inoculated cultures were reported as showing growth if they contained at least 50 colonies after five weeks of incubatic Problems of drug resistance cannot be confined

the necrotic area is seldom cleanly sloughed the cavity wall is composed to some extent of necrotic lung tissue This situation makes complete healing of a cavity by scar formation difficult and leaves on closure of the cavity an area of necrotic material surrounded by scar tissue with the patent connecting bronchus remaining or only plugged by inspissated debris Such a filled in cavity can again become an open cavity if the inspissated contents become sufficiently fluid to flow



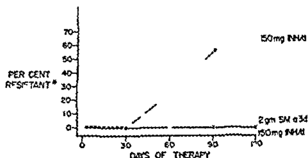
Fig 39 (C t f Ry B J et l J Th S g 23 3 7 340 Ap l 1952)

down the bronchus The common persistence of the unhealed necrotic pneumonic tuberculous lesions in persons who have become clinically well is the cause of relapses These necrotic lesions usually harbor living bacilli for a long time and the bacilli can be present in tremendous numbers even if they are not demonstrable in sputum

The behavior of these necrotic lesions contrasts with that of the areas of reversible tuberculous pneumonia which heal with bed rest and chemotherapy Because of this Bernard J Ryan Edgar M Medlar and Edward S Welles[5] (V A Hosp Sunmount N Y) subjected 30 patients to local excision of the lesions after prolonged therapy had produced maximal

(5) J Th S g 3 3 7 340 Ap l 195

with any exact level of isoniazid resistance experience with other antituberculous drugs would indicate that development of a several fold increase in bacterial resistance may limit the therapeutic effectiveness of this agent Knowledge of other combined drug regimens suggests that the administration of streptomycin or other antituberculous agents with isoniazid may delay the emergence of bacterial resistance to both drugs



C ltu es n g owth on 1 µg INH/ml q l to c ntrol e t trar ly lled esistant Pe ntag cal lat d in t ms of n mber f pati nt w th known drug sens t v ty at t me of luation

F g 38—Em g c f b t rial res stan e dur ng b ter al valuat on f so n a d and ison d t eptomyc n eg m ns f l min y eport based on analys s S pt 4 195 (Court of Dye W E *et al* Am R v Tube 67 106 107 Janu ary 1953)

William E Dye Helen P Lynch and Atlanta G Brees[4] (Fitzsimons Army Hosp) reproduce bacteriologic data from a preliminary report comparing isoniazid therapy with combined isoniazid intermittent streptomycin therapy (Figs 37 and 38) The emergence of bacterial resistance during daily isoniazid therapy appeared to be appreciably delayed by concomitant intermittent streptomycin therapy

Simple Excision in Treatment of Pulmonary Tuberculosis Caseous tuberculous foci especially those located in the upper and posterior portions of pulmonary lobes are the causes of clinical relapses of this disease These necrotic lesions or tuberculous abscesses may soften up and slough into the connecting bronchus early or may remain with the dead framework of the lung intact within the necrotic zone for many months A discharge of the softened necrotic debris into bronchi leads to formation of the tuberculous cavity and since

(4) Am Rev Tuberc 67 106 107 January 1953

the necrotic area is seldom cleanly sloughed the cavity wall is composed to some extent of necrotic lung tissue This situation makes complete healing of a cavity by scar formation difficult and leaves on closure of the cavity an area of necrotic material surrounded by scar tissue with the patent connecting bronchus remaining or only plugged by inspissated debris Such a filled in cavity can again become an open cavity *if the inspissated contents become sufficiently fluid to flow*



Fg 39 (C t y f Ry B J et l J Th Su g 3 3 7 340 Ap l 1952)

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(5) J Th S g 23 327 340 Ap l 1952

healing and sputum and gastric contents from which no tubercle bacilli could be cultured Four patients had had minimal 16 moderately advanced and 10 far advanced diseas Usually only wedges of lung were resected although on occa sion the removal of an entire lobe or a lung was necessary

Tuberculin reaction in man 27 was positive on June 26 1947 whereas it had been negative less than a year previously No abnor mal shadow was seen in the roentgenogram at that time but was first noted at the right apex on Nov 10 1948 (Fig 39) The shadow persisted after one year of bed rest and an additional four months of combined streptomycin and PAS therapy A wedge of necrotic tuberculous tis ue (minimal lesion) was removed from the apex of the right upper lobe and he received both drugs postoperatively for four months Since Jan 1 1952 he has been working full time

The wedge of lung removed measured about 2 5 cm across Serial section of the entire specimen howed six separate lesions two of which were largely car tissue In one of the carred areas was an organizing old necrotic focu which was interpreted as the initial necrotic lesion from which the others were disseminated Three of the lesions showed a peripheral organizing zone of granu lation tis ue and a central core largely compo ed of neutrophils Tubercle bacilli in small numbers were found in the exudate in these lesions but not in the scarred areas Only occasional epithelioid tubercles and giant cells were found in the serial sections

Each resected specimen showed necrotic pneumonic lesions and the cavity bearing areas removed showed filled in cavities with patent bronchial communications Otherwise there were areas of scarred tissue with little evidence of unhealed non necrotic pneumonic lesions The bronchi at the resected end of the wedge showed little evidence of disease other than some lymphocytic infiltration of an intact mucosa Tubercle bacilli were found in one or more although not in all necrotic lesions in every instance Patent bronchial communications with some necrotic lesions were apparent microscopically although not macroscopically

Postoperatively 205 cultures of sputum or gastric contents for tubercle bacilli gave negative results There was little change in the cardiorespiratory reserves postoperatively No postoperative tuberculous complications arose and no compli cations of any sort occurred in the four patients with minimal disease As a rule the postoperative course was benign and all patients remained in excellent physical condition Post operative complications were limited to hemothorax atelec

tasis and inadvertent division of the phrenic nerve each in one case

[The removal of relatively small residual necrotic lesions according to the principles and for the indications set forth here has become a controversial issue As the authors themselves point out a minimum of five years may be necessary to assess the results At the present time the force of the proponents arguments are weakened by two sets of observations The first is that the bacilli which are often easily demonstrable microscopically in the resected lesions, frequently fail to grow on culture mediums or to infect experimental animals at least when this is attempted by the usual technics Irrespective of whether or not the bacilli are actually no longer viable under these circumstances they are evidently altered biologically in a manner which is apparently favorable to the host The other consideration is that the relapse rate of comparable cases treated without excision but with long term chemotherapy has not been shown so far to be materially greater than in those subjected to surgery Relapse rates of conservatively treated minimal tuberculosis before the introduction of long term chemotherapy are variously reported from 10% to 30% Such relatively high relapse rates cannot be assumed however for the best present day conservative treatment—Ed]

Segmental Resection in Surgical Treatment of Pulmonary Tuberculosis Clifford F Storey and Bruce F Rothmann[6] (U S Naval Hosp St Albans N Y) report on 130 patients operated on in four years and followed at least six months 17 (13 1%) had a pneumonectomy 25 (19 2%) lobectomy and 88 (67 7%) segmental resection There were three deaths (3 4%) Two patients died in the hospital Neither death was directly attributable to tuberculosis or to the type of operation performed one patient died of an anesthetic accident and the other of lower nephron nephrosis possibly the result of a transfusion reaction The third death occurring long after the patient s discharge resulted from an unrelated cause tuberculosis appeared to be arrested at the time

The percentage of major complications was 15 5% although the percentage of patients with such complications was much smaller For example reactivations occurred exclusively in patients in whom a bronchopleural fistula with empyema developed Bronchopleural fistulas occurred in 4 5% spread in 3 4% and reactivations in 3 4% Minor complications totaled 27 1% those most frequently encountered were localized apical pneumothorax (9%) persistent air leak (8%) and atelectasis (5 7%) There was one case each of hemothorax thrombophlebitis parotitis and trochanteric bursitis

(6) J I t t C ll S g 19 53 68 J ry 1953

Four of 84 surviving patients had "positive" sputum on culture. Of the four, two had bilateral disease and each had had a contralateral thoracoplasty. The authenticity of the single result from a sputum culture in one case is doubted and detailed hospital investigation of the other patient failed to establish the source of the intermittently positive results of sputum cultures.

Twenty five patients (28.7%) remained in the hospital. 38 of the 59 discharged patients who survived were gainfully employed. Many of the others, although apparently well and able to work, had been advised not to do so as a precautionary measure. Thus 93.2% of the surviving discharged patients or 91.7% of all discharged patients were considered physically fit for employment.

Segmental resection is a useful addition to the surgical methods used in treatment of pulmonary tuberculosis. Careful case selection, patient preoperative preparation, accurate timing of the surgical procedure, skilful surgical technic and meticulous postoperative care are required. When these tenets are adhered to strictly, a high percentage of successes can be anticipated; if they are violated, the rate of complications will increase, the number of satisfying results will decrease and the operation will fall into disrepute.

Segmental Resection in Tuberculosis. Richard H. Overholt, Francis M. Woods and Norman J. Wilson[7] (Tufts College) report on 125 patients operated on in 1947-51 and followed for 6 months to 4½ years. In those who had had previous surgery or collapse therapy (pneumoperitoneum excluded), resection was designated as "secondary" and when it was the first surgical procedure as "primary."

Results after primary segmental resection were excellent in 92% of the original treatment group and 96% of living patients classified as clinically well with negative sputa. However, the results are not a measure of the effectiveness of the operative procedure alone. They are secured only when segmental resection is used in a select group with initial or residual necrotic lesions well contained within segmental boundaries. Such patients are in good general condition, in immunologic balance with the disease and usually have been treated intelli-

(7) Dis. Chest 23:255-265, Mar. 1953.

gently with bed rest and antimicrobial drugs Excellent results are inevitable since a high percentage of such patients can be treated successfully by other measures

By contrast results of segmental resection as a secondary procedure were poor and indicated that segmental resection in certain circumstances can be the most dangerous of all resections When segmental planes are obliterated and adjacent segments contain nodulation and emphysema or when the segment to be removed contains the residual cavity but there is widespread nodulation throughout the rest of the lung tissue results will be poor When preservation of function and lung volume are vital if respiratory reserve is marginal segmental resection may be justified but the possible gain in function must be weighed against the increased risk Under certain conditions lobectomy is a much safer operation than segmental resection and thoracoplasty is often safer than either

Results of lobectomy and pneumonectomy compared favorably with those of segmental resection They showed that good results can be expected with any type of resection provided there is (1) adequate respiratory reserve (2) the lesion is well confined within the limits of the unit of lung to be excised (3) resection is primary and (4) resection is performed on attaining ideal conditions with bed rest and antimicrobial drugs

Late Results of Pneumothorax Therapy The value of pneumothorax therapy was probably overestimated 20 years ago when its indications were not well defined The consequent poor selection of cases and other factors have led to present underestimation of its value in appropriate cases Jack H Rubin and Hugh E Burke[8] (Royal Edward Laurentian Hosp Montreal) obtained favorable results without the usually cited complications (bronchopleural fistula empyema) by applying the following principles (1) cauterization of adhesions early in the course of pneumothorax or if the adhesions cannot be safely and satisfactorily severed prompt discontinuance of therapy (2) maintenance of a selective collapse rather than allowing a large portion of or the entire lung to collapse (3) maintenance of pneumothorax for a sufficient period

Late results in 120 patients are presented No streptomycin was given during or after collapse therapy Patients in whom

[8] C M A J 66 447 451 May 1952

it was impossible to establish an effective pneumothorax or in whom complications occurred during early stages of treatment were excluded Most patients had moderately far advanced pulmonary tuberculosis when pneumothorax was initiated (table) On the average this therapy was maintained for 30 months in minimal cases 63 3 months in moderately far advanced cases and 65 5 months in far advanced cases Lungs which had been kept partially collapsed even for such long periods could be re expanded without undue difficulty

EXTENT OF PULMONARY TUBERCULOSIS AND SPUTUM FINDINGS BEFORE PNEUMOTHORAX

Extent of Disease	Cases	Sputum Pos for M Tuberculosis	Sputum Neg for M Tuberculosis	No Report
Minimal	6	3	3	–
Moderately far advanced	110	79	27	4
Far advanced	4	3	1	–
Total	120	85 (70 8%)	31 (25 9%)	4 (3 3%)

and seemingly little loss of respiratory efficiency Of 112 patients still living two to seven years after cessation of therapy 106 were well with inactive tuberculosis Of these 6 had minimal 99 moderately far advanced and 1 far advanced tuberculosis before pneumothorax The six other living patients had active tuberculosis and were in the moderately far advanced group before therapy Of the 106 patients who were well 56 presented clearly defined x ray signs of cavity at the time pneumothorax was initiated In general pneumothorax was maintained for longer periods in patients whose chest x rays disclosed signs of cavity before therapy was begun Of the eight patients who died five had had moderately far advanced and three far advanced tuberculosis before pneumothorax

Pneumothorax can be used in certain selected cases in which bed rest and chemotherapy do not appear to give promise of arresting the disease and in which perhaps the extent and the nature of the tuberculous process or the patient s general condition do not warrant major surgery Fewer failures will result if unsuitable cases (those of far advanced bilateral disease especially with fibroid lesions thick walled cavities emphysema and pleural synechiae) are eliminated and if it is ascertained that no endobronchial tuberculosis is present

[Pneumothorax therapy has fallen into almost complete disuse in many sections of this country and is everywhere giving ground even in highly suitable cases to excisional procedures This report of late results of pneumothorax prompts the question whether the pendulum has not swung too far The results are particularly impressive when it is noted that these are patients whose pneumothorax therapy was discontinued during 1941 1946 before the era of streptomycin and the treatment was carried out without the protection of any antimicrobial therapy It remains to be seen whether excisional therapy even under the protection of antimicrobial therapy will produce equally good late results in comparable cases —Ed]

Appraisal of Protective Value of BCG Vaccine Joseph D Aronson and Charlotte Ferguson Aronson[9] (Univ of Pennsylvania) studied the value of BCG vaccine in controlling tuberculosis in Indians of the United States and Alaska School and preschool age children with negative reactions to tuberculin were placed in two groups comparable in numbers age and sex Members of one group received a single intracutaneous injection of freshly prepared BCG vaccine and were not revaccinated during the study Those in the control group received an intracutaneous injection of isotonic sodium chloride solution Neither group was isolated before or after vaccination and no change was made in the mode of living Both groups were examined annually for 9 11 years by means of tuberculin tests and chest x rays

Mortality was determined 15 years after the study was initiated The cause of death was determined by roentgen and laboratory examinations clinical records nurses notes and personal interviews with relatives in the few cases in which diagnosis had not been established In no instance was the death certificate diagnosis accepted without further careful investigation During the 13 15 years of observation 71 vaccinated persons and 128 controls died Among the 1 551 vaccinated persons observed for a total of 21 245 5 person years 12 died of tuberculosis a rate of 0 56 per thousand person years of observation Among the 1 457 controls observed for a total of 19 520 5 person years 65 died of tuberculosis a rate of 3 32 per thousand person years Fifty nine vaccinated persons and 63 controls died of nontuberculous causes rates of 2 77 and 3 22 per thousand person years of observation respectively Of the 12 tuberculosis deaths among the vaccinated group 6 were due to pulmonary tuberculosis 2 to

(9) J A M A 149 334 343 May 24 1952

bone and joint tuberculosis 3 to tuberculous meningitis and 1 to tuberculous meningitis and pulmonary tuberculosis Among the 65 unvaccinated controls dying of tuberculosis 32 died of pulmonary tuberculosis 2 of bone and joint tuberculosis and 31 of acute miliary or similar forms of tuberculosis including tuberculous peritonitis Tuberculin reactions of the controls dying of acute forms of tuberculosis were for the most part negative or had become positive for the first time within the year of death

The data support the concept that there is a close but not absolute relation between resistance to reinfection and hyper sensitivity Hypersensitivity among the vaccinated persons of whom 12 died of tuberculosis ranged from 93 3% one year following vaccination to 90 2% 11 years later Among the controls 65 of whom died of tuberculosis hypersensitivity in creased from 12 7% one year after the initiation of the study to 41 7% after 11 years

[The difference between the tuberculosis death rates of the vaccinated and the control groups will be repeated here for emphasis They are 0 56 per thousand person years of observation for the vaccinated 3 32 per thousand person years for the controls The ratio is one death in the vaccinated to five in the unvaccinated This hould convince those who still doubt the advisability of BCG vaccination for groups whose risk of exposure to tuberculosis is high—Ed]

MISCELLANEOUS

Asymptomatic Arteriovenous Fistula of Lung Report of Case with Surgical Care A group of signs and symptoms has been built around the diagnosis of pulmonary arteriovenous fistula This diagnosis is considered whenever a patient in the absence of congenital heart disease has cyanosis clubbing of the fingers and toes and polycythemia However the lesion can be entirely asymptomatic It may masquerade as a benign appearing shadow in the pulmonary parenchyma detected only by chance roentgenograms Theodore J Talbot and Jacob J Silverman[1] (Staten Island Hosp) report such a case in a man 48 in whom a noncharacteristic nodule discovered acci dentally at a routine x ray examination of the chest was cor rectly diagnosed by lateral tomography Presence of the fistula was confirmed by thoracotomy

(1) A M A Arch Int Med 90 569 574 Oct be 1952

Since the course of pulmonary arteriovenous fistula is notoriously unpredictable diagnosis should be established early and surgical treatment given Instances have been reported in the newborn but diagnosis usually is not established until after puberty The fistulas enlarge at varying rate in different persons Fatalities may occur at any time from uncontrollable pulmonary hemorrhage Thrombosis at the site of the fistula and subacute bacterial endocarditis are also serious threats to life

[An important possibility in the differential diagnosis of asymptomatic isolated parenchymal lesions found in routine roentgenographic examinations of the chest The value of lateral tomograms was strikingly demonstrated in this instance in which a correct preoperative diagnosis was made without the assistance of angiocardiography —Ed]

Eosinophilic Granuloma of Lung Robert W Lackey Frank Y Leaver and Charles J Farinacci (Fitzsimons Army Hosp) describe two cases of eosinophilic granuloma limited to the lungs and a case of eosinophilic granuloma of bone with pulmonary findings Clinical signs were mild but two of the three patients had lost considerable weight Histopathologically the lesions in the lungs were identical with eosinophilic granuloma of bone

The roentgen findings are identical with those of Letterer Siwe Hand Schuller Christian and Gaucher s diseases and other xanthomatoses Lung changes are diffuse and generalized consisting of a granulomatous infiltrate nodular in character The nodules varying in size from miliary dimensions up to 1 5 cm in diameter are not sharply demarcated but have hazy borders fading into the normal lung tissue surrounding them There is evidence of associated localized areas of emphysema and fibrosis Findings were identical in the two patients without extrapulmonary involvement

It is suggested that the two cases of localized pulmonary eosinophilic granuloma like eosinophilic granuloma of bone represent a monosymptomatic form of a systemic xanthomatous disorder and that the term eosinophilic granuloma be expanded to include cases in which there are extraosseous lesions such as those involving lungs skin and other organs

Pulmonary Eosinophilia The term Loffler s syndrome has often mistakenly been applied to a poorly defined group of diseases in which at some time infiltrations are observed

(2) R d logy 59 504 513 O t b 195

radiologically and are accompanied by eosinophilia Since the syndrome includes only a section of this group J W Crofton J L Livingstone N C Oswald and A T M Roberts[3] (Brompton Hosp London) suggest the term pulmonary eosinophilia to describe the entire group The definition of pulmonary infiltration with blood eosinophilia is not in itself absolute Certain patients have eosinophilia in some of their attacks but not in others which are in every other way identical Again in tropical eosinophilia which should be included in the group there may or may not be pulmonary infiltrations This *definition* covers a wide range of diseases forming a continuum from mild true Loffler s syndrome to severe polyarteritis nodosa with lung involvement They may be classified as (1) simple pulmonary eosinophilia or Loffler s syndrome *transient infiltrations* (2) prolonged pulmonary eosinophilia *prolonged or recurrent infiltrations* without asthma (3) pulmonary eosinophilia with asthma infiltrations with asthma (4) tropical pulmonary eosinophilia usually with asthmatic symptoms (5) polyarteritis nodosa Tropical eosinophilia is a well defined group and its relation to the rest of the continuum is uncertain

In Loffler s syndrome symptoms are mild or absent and abnormal physical signs are only detected with difficulty Abnormal shadows in the lung fields are always shown on the x ray but these disappear in 6-12 days Transient eosinophilia *is essential to diagnosis Cough is the commonest symptom* although it is often absent There is often no fever when present it is usually mild although temperatures up to 104 F have been recorded The x ray shadows are usually fan shaped and fairly homogeneous but have indefinite borders These may be uni or bilateral and may disappear in one part of the lung to appear in another Infestation with Ascaris lumbricoides is by far the commonest etiologic factor Infestation with other worms or miscellaneous allergens are at times responsible That Loffler s syndrome is ever due to tuberculosis seems doubtful

In prolonged pulmonary eosinophilia infiltrations persist for over a month Seventeen cases in patients aged 2 58 have been described in the literature The picture varied in severity but often the illness was less severe than the temperature chart

(3) Tho x 7 135 Ma ch 195

(up to 103 F) would suggest Fever often lasts for a month X ray changes varied from indefinite localized mottling to a relatively homogeneous shadow occupying most of the lung field Maximal eosinophilia varied from 10% of a total white cell count of 10 800 to 72% of a total count of 117 000 The illness usually lasts two to six months although some patients recovered in six weeks In only 4 of the 17 cases was there no evidence of an etiologic factor (parasitic microbial or fungus infection) or an allergic diathesis

Tropical eosinophilia is sometimes characterized by an initial stage of malaise fever coryza and dry cough lasting from one week to a month During this phase the spleen may be palpable The bronchitic aspect then becomes prominent and may continue for months It is followed by an asthmatic phase with pronounced wheezing which may last months or years although at any time the condition may resolve spontaneously In perhaps half these cases the x ray if taken one to six months after onset will show a diffuse mottling throughout both lung fields though sometimes the lesions are more localized There may be hilar glandular enlargement especially in children There is always a gross eosinophilia The total white cell count is almost always over 15 000 often 50 000 or more and the eosinophil count varies from 20 to 90% Administration of organic arsenic results in clinical cure in most cases often within a few days In one reported case administration of adrenocorticotrophic hormone produced some lowering of the eosinophils count but no change in the x ray picture The cause of tropical eosinophilia is not established although there is evidence incriminating mite infestation of the respiratory tract

A large number of cases have been reported in which pulmonary infiltrations and eosinophilia were associated with asthmatic symptoms Usually the occurrence of pulmonary infiltrations was only an incident in chronic or recurrent bronchial asthma but some patients had asthmatic symptoms only while the pulmonary infiltrations were present In a few although they had a history of asthma no asthmatic symptom occurred when the infiltrations were observed

Although lung changes are frequently seen at autopsy in cases of polyarteritis nodosa there are only a limited number of proved cases recorded in which eosinophilia was asso

ciated with x ray evidence of pulmonary *infiltrations* About two thirds of the patients had asthma Some had had it for a long time but others had symptoms only during their final illness

Pleural effusions containing a high proportion of eosinophils may occur in any of the subgroups of pulmonary eosinophilia It seems probable that on occasion the effusion may obscure an underlying lung lesion and the case present as one of primary eosinophilic pleural effusion Such cases should probably be included in the syndrome of pulmonary eosinophilia

This syndrome represents a peculiar reaction of the body to various stimuli This reaction can be regarded as one of hypersensitivity although some of the allergens are probably capable of producing a reaction in most persons When the hypersensitive reaction is brief and involves only the alveoli the manifestation is a simple pulmonary eosinophilia as described by Loffler when it is more prolonged it may be called prolonged pulmonary eosinophilia When the bronchi are also involved the condition becomes pulmonary eosinophilia with asthma or possibly when the precipitating factor is a bronchial infestation with mites tropical eosinophilia If in addition there are gross lesions of the blood vessels there will probably be lesions of other organs and the condition may go on to the full picture of polyarteritis *nodosa*

Acute Diffuse Interstitial Fibrosis of Lungs is discussed by William P Callahan Jr John C Sutherland John K Fulton and John R Kline[4] (Wichita Kan) who report a case in which the clinical signs and symptoms and the roentgen findings were analogous to those previously described in this disease Diagnosis was made after studies of autopsy material In 16 reported cases there was no predominance of the disease in one sex or in any racial or age groups Ages ranged from 21 to 68 (average 44) Occupation apparently was not important and did not imply contact with any specific toxic agent In six cases there was a prodromal period (six months to seven years) with nonproductive cough weakness and weight loss Incomplete clinical studies during this period disclosed no clinical signs or roentgen evidence of pulmonary disease Histories of all patients failed to indicate pre existing pulmo

(4) A M A Arch Int. Med. 90 468-48 October 195

nary disease which might have led to pulmonary fibrosis or a preceding viral or atypical pneumonitis No bacterial agent could be incriminated as a possible etiologic factor Fever was present in only one patient during the prodromal period and in most patients (all on antibiotic therapy) this symptom was absent during the entire disease Leukocytosis occurred sporadically throughout the disease but was not persistent and was usually terminal Sputum of the authors patient never contained the purulent material which indicates suppurative inflammation in the tracheobronchial tree These findings suggest that the disease does not arise from previous or concomitant bacterial infection

During the active phase of the disease there were increasingly severe dyspnea cyanosis and occasional hemoptysis Roentgenograms showed progressive dissemination of peribronchial densities usually beginning in the lower lobes and extending to involve the entire lungs In six patients there were hypertrophy and dilatation of the heart and thickening of the myocardium of the right ventricle Although in the authors case no enlargement of the heart was observed the extensive deposition of fibrinous material within the alveoli without anatomic evidence of an exudative process indicated terminal pulmonary edema and transudation of a fluid high in protein content into the alveolar spaces Serum protein content fell precipitously probably because of accumulation of protein in the alveolar spaces Roentgen findings similar to those previously reported consisted of peribronchial thickening beginning at the bases and within two weeks extending to all lobes The rapid progressive increase in density was undoubtedly a result of interstitial fibrosis but may have resulted partly from accumulation of fibrinous material in the alveolar spaces The rapid progression of the lesions would be unusual in any but an inflammatory disease The peribronchial spread of primary or metastatic tumors Hodgkin s disease lymphosarcoma and sarcoidosis does not develop so rapidly The roentgen findings associated with the symptoms of cough hemoptysis and dyspnea with progressing cyanosis are sufficient to establish a clinical diagnosis

The anatomic findings in this case as in those previously reported imply a single pathologic process with production of various physiologic disturbances The fundamental patho

logic change was an increase in interstitial connective tissue with impairment of the blood flow through the lungs The subsequent development of interstitial edema and transudation of fluid into the alveoli interfered with the gaseous exchange and was responsible for clinical symptoms of dyspnea and cyanosis Peripheral emphysema results in uninvolved portions from hyperpnea and excessive respiratory efforts

Complete lack of cellular infiltration implies that the basic lesion was not bacterial and if inflammatory must have resulted from viral infection or chemical irritation which could not be excluded although no definite history of exposure was obtained Production of fibroblasts is the most common response to the presence of lymph in the intercellular spaces but is usually associated with chronic obstruction to lymph flow and such lesions have been obtained experimentally in subcutaneous tissues by producing obstruction in regional lymphatic channels Such a hypothetical sequence of events may be a factor in the development of the changes in the interstitial tissues of the lung This type of pathologic change could explain the prodromal stage and the acute phase of the disease

Boeck's Disease (or Sarcoid) and the Tubercle Bacillus According to Olav Refvem[5] (Univ of Oslo) although the histologic picture of Boeck s disease is characteristic and forms an essential basis for the diagnosis the picture is not specific and can be produced by a number of bacteria fungi protozoa plants and chemical substances Consequently the diagnosis of Boeck s disease may be uncertain despite typical histologic manifestation Cases due to agents other than the tubercle bacillus are often classified as symptomatic the view being that all genuine cases are caused by the tubercle bacillus However tuberculous cases comprise only a small fraction of the numerous cases in which no causative agent can be identified

In 1921 Kyrle reported a case of generalized sarcoid skin lesions which appeared in three distinct periods regressing completely spontaneously after eight three and three months Numerous biopsy studies were made during the second and third period Tubercle bacilli were found in stained sections in the early stages of the sarcoid lesions up to and including the 21st day but not from the 36th day Sarcoid tissue con

(5) A t t be c sca d na 27 314 326 1952

taining tubercle bacilli produced no reaction in guinea pigs but animal experiments suggested that the patient s blood contained virulent tubercle bacilli Kyrle concluded that sar coid is caused by tubercle bacilli and that the bacilli are rap idly destroyed in sarcoid tissue thereby explaining failure to recover the tubercle bacillus in this disease

There are objections to this view Kyrle s case is so peculiar clinically especially in the two closely observed attacks as to prove little with respect to Boeck s disease The hematuria between the last two periods might be attributed to tubercu losis of the kidney from which massive but brief influxes of tubercle bacilli into the blood may have resulted in acute miliary tuberculosis On the other hand the first and more lengthy phase of the disease may really represent Boeck s dis ease Furthermore clinical course as well as autopsy observa tions indicate an active process not a sequel Some lesions disappear new ones develop Kyrle s explanation seems in applicable to the relatively common cases presenting only a single or a few sarcoid lesions of the skin which show con tinual growth over many years In such cases tissue from the peripheral area would represent an early stage and conse quently contain tubercle bacilli This leads to the improbable concept of virulent organisms produced in one tuberculous focus in the body being disseminated widely and some finding their way to the sarcoid where they produce noncaseating tuberculosis Actually a caseating focus is seldom found at autopsy

Even generalized forms of the disease are not satisfac torily explained as chronic miliary tuberculosis The mere existence of a pathologic condition that in some cases is barely distinguished from Boeck s disease does not prove identity Furthermore the tuberculin reaction is seldom negative in chronic miliary tuberculosis That some patients with general ized Boeck s disease become allergic to tuberculin after a single injection of BCG vaccine is hardly compatible with the assumption that the system is already over run with tubercle bacilli Few cases in which tuberculous etiology of Boeck s disease has been claimed will stand close investigation The fact that patients with Boeck s disease often have serious caseous tuberculosis indicates a relationship but does not prove a common etiology Boeck s disease may like measles

silicosis and various other diseases have an unfavorable effect on tuberculosis The finding of transition forms between caseating and noncaseating tubercles is no proof that Boeck s disease is nothing but a special phase of tuberculosis The following observation casts some light on the relation between Boeck s disease and tuberculosis

Woman 52 had had typical Boeck s disease for 18 years Tuberculin reaction was consistently negative to even the largest dose —3 mg OT When 0 05 mg BCG was injected intracutaneously into the left thigh a papule formed which soon disappeared without alteration in the tuberculin reaction Ten weeks later when a double dose of BCG was injected into the right thigh the papule formed and remained unchanged for 3½ months Redness tenderness and an infiltration the size of a child s hand suddenly appeared around the papule 15½ weeks after inoculation The patient complained of pain in the right groin felt ill and had slight fever In a few days skin necrosis and an abscess formed which did not respond to penicillin The infiltration receded gradually and spontaneously to healing in five or six weeks Pus from the lesion cultivated on Loewenstein s medium yielded numerous colonies of tubercle bacilli which when injected in guinea pigs and rabbit caused no macroscopic signs of tuberculosis indicating no increase of virulence of the BCG strain Two weeks after the violent reaction an intracutaneous test with 1 mg OT caused 10 mm redness and 8 mm infiltration A few days later she was tuberculin negative and remained so The sarcoid lesions in the skin were unaltered throughout

This case indicates that even nonvirulent tubercle bacilli can survive four or five months in the skin of a patient with Boeck s disease That tubercle bacilli only rarely are found in the sarcoid tissue can therefore not invariably be attributed to rapid destruction of the bacilli as Kyrle assumed To what extent sarcoid patients react as tardily to virulent tubercle bacilli as this patient did to BCG is not known

The delayed allergic reaction to tubercle bacilli in patients with Boeck s disease may be the key to their tendency to serious tuberculosis In fact there is evidence of slow mobilization of the body s defense mechanism which is first completely developed with the onset of allergy During the preallergic period multiplication of tubercle bacilli is relatively undisturbed i e at an accelerating tempo Consequently the chances of serious development are probably particularly great when the allergic reaction is weak Tuberculin negative as well as tuberculin positive sarcoid patients should be carefully protected against exposure to exogenous infection from tubercle bacilli and they should not be treated in tuberculosis sanatoriums

Alcohol Oxygen Vapor Therapy of Pulmonary Edema Results in 50 Attacks Morton A Goldmann and Aldo A Luisada[6] (Chicago) report on 45 patients who were given ethanol oxygen vapor (E O V) by inhalation for 50 attacks of which 40 were paroxysms Administration of 95% alcohol by nasal catheter is most suitable for conscious patients and was used in 36 attacks Conventional equipment was used with the nasal catheter the 95% alcohol placed in the humidifier and oxygen flow gradually raised to 7 10 L/minute Admin istration of 30-40% alcohol by mask is more convenient in unconscious patients and was used in the other 16 attacks Administration by oxygen tent was less efficient and made the environment uncomfortable for the patient

Inhalation of E O V was used exclusively in 14 attacks with excellent frequently dramatic improvement in 12 (85%) Maximal benefit usually occurred within an hour It was used after failure of conventional therapy in 25 attacks (13 very severe 9 severe 1 moderate) objective improvement occurred in 15 (promptly in 12 of them) Six other attacks responded similarly but a waning effect of previous therapy could not be altogether discounted

Of 35 patients with acute pulmonary edema (40 attacks) 7 died 5 had been clinically relieved of the edema but died of other causes Ten patients presented a less dramatic variant of pulmonary edema more insidious in onset and more pro tracted in its course Results of therapy in such subacute pul monary edema are even more difficult to evaluate than in the acute form Five patients were 70 or older and all were in very poor or terminal state when E O V therapy was initiated None was considered likely to survive Improvement was good in three moderate in two and minimal in two the other three failed to improve Six of the 10 patients died subsequently of the underlying condition

Tolerance was excellent in 47 of 50 attacks Bronchoscopy performed in one patient as a clinical experiment failed to reveal untoward local changes In control subjects only min imal absorption of alcohol was revealed by blood determina tion

There are few contraindications In patients receiving tetra ethylthiuram disulfide the blood alcohol concentration may

(6) A I t M d 37 1 21 1 31 D emb 1952

approach dangerous levels Judgment must be reserved as to possible contraindication in acute pulmonary edema due to irritating gases

Ethyl alcohol by inhalation has been considered the agent of choice for pregnant women and for patients in shock (including coronary patients) or with central nervous system lesions Since it can be used in conjunction with other measures and frequently succeeds where other procedures fail the method should be given an extensive trial in all cases of acute pulmonary edema and in selected cases of subacute pulmonary edema

THE BLOOD
and BLOOD-FORMING ORGANS

WILLIAM B CASTLE M.D

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS AND SPECIAL TECHNICS

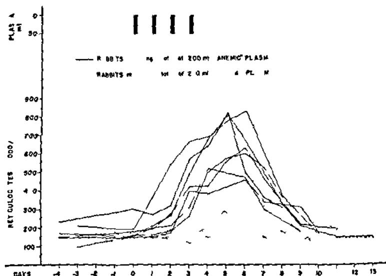
Humoral Regulation of Red Cell Production. Allan Erslev[1] (Yale Univ) states that it is generally accepted that the oxygen content of arterial blood regulates erythropoietic activity but whether this regulatory effect is exerted on the bone marrow directly or through an intermediary humoral factor is still unknown Recent experimental evidence has weakened the hypothesis that the oxygen content affects the bone marrow directly Oxygen tension and saturation of bone marrow have been shown by Grant and Root to be normal in dogs in which increased erythropoiesis was induced by acute and chronic bleeding Normal oxygen saturation of bone marrow blood was also found in patients with various chronic anemias and with polycythemia vera Birkhill has emphasized that the amount of oxygen delivered to the bone marrow probably is more important than the oxygen tension of the bone marrow in regulating red cell production Tinsley *et al* have stated that it is hard to believe that normoblasts which consume large amounts of oxygen should be stimulated to increased activity by decreasing their supply of oxygen Tissue culture studies have indicated that anoxia of bone marrow cultures caused depression and arrest rather than an increase in normoblastic activity

In 1906 Carnot and Deflandre suggested that blood oxygenation regulates red cell production by means of an intermediary factor According to this theory the arterial blood oxygen regulates the production of a factor capable of stimulating erythropoiesis This factor is carried to the bone marrow by the blood stream They injected 9 cc of plasma obtained from

(1) Blood 8 349 357 Ap 1 1953

slightly anemic rabbits into normal rabbits and noticed a small rise in the number of red cells in the peripheral blood Plasma from severely anemic rabbits did not have any effect on the red blood cell count

The present study was made to secure definite information as to the presence or absence of a plasma factor capable of stimulating red cell production A large amount of plasma from rabbits made anemic by bleeding was injected into normal



F g 40 —Ret l yt sponse n ch of s en bb ts r g pl m f om an m c do r nd n each f bb ts r g pl m f m n m l d or (Court y f E lev A Blood 8 349 357 Ap l 1953)

rabbits As a control the same amount of plasma from normal rabbits was used The resulting effects on red cell production were compared Figure 40 shows the reticulocyte counts in seven rabbits receiving 50 cc plasma from anemic donors once a day for four days and in six rabbits receiving 50 cc plasma from normal donors once a day for four days The anemic plasma consistently produced a significant reticulocytosis The injection of the anemic plasma also caused an increase in the red cell count and the hematocrit value Rabbits given anemic plasma had erythroblastic hyperplasia of the bone marrow

The study strongly supports the theory that red cell pro duction is controlled at least to some extent by an intermediary humoral factor There was no change in the white blood cell count or platelet count in two rabbits in which 13 injections of plasma from anemic donors had caused a significant increase in red cell production However it is possible that larger amounts of the stimulating factor in plasma from anemic donors over longer periods may affect granulocyte and platelet production

[Such humoral factors may also be involved in the production of sec ondary polycythemia and conceivably in the protective effect of shielding the spleen from x ray exposure —Ed]

Influence of Drugs on Blood and Bone Marrow Frank J Heck (Mayo Clinic) states that drug therapy can be incrim inated in the reproduction of practically every known type of blood dyscrasia In the introduction of new drugs it is necessary to consider critically their possible effect on the blood and bone marrow Careful observation of and report on the blood changes that occur in the number of cases ordi narily reported in trials of drugs cannot be considered an adequate basis for determining whether a particular drug has a harmful effect since sensitivity to any of these drugs is uncommon When there is a choice among several drugs all of which have the same therapeutic effect but one of which affects even the occasional patient in a harmful manner that drug must be excluded from consideration in therapy Many drugs which may have a damaging effect on the bone marrow are being used in practice every day As long as these drugs are the only ones available for specific purposes and the risk from the disease being treated is greater than the risk of using the drug the physician is warranted in taking the calculated risk involved

One of the most easily recognized blood dyscrasias due to drugs is granulocytopenia (mortality rate 60 90%) which occurs mostly in women and has an acute onset with chill fever commonly sore throat aching of the bones and a pro gressive decrease in the total leukocyte count with simulta neous decrease or disappearance of the neutrophils Ulceration of the mucous membranes is frequent Drugs commonly in volved are aminopyrine and sulfonamides The only treatment is with antibiotics which may protect certain persons who might otherwise die of an infection

(2) P tg d M d 33 185 193 M h 1953

Thrombocytopenic purpura may be induced by drugs e g acetarsone aminopyrine arsphenamine benzene ergot gold salts nitrogen mustard quinidine quinine sedormid® stilbestrol and sulfonamides Thrombocytopenia and purpuric manifestations may appear during the time of ingestion of the drug and disappear when the medication is stopped or the symptoms and findings may not appear until some time after *medication has been given*

Hemolytic anemia may be caused by acetophenetidin ammonia arsphenamine hydrogen arsenide hydroquinone phenothiazine phenylhydrazine plasmochin® and quinine The anemia may be precipitated acutely or may have a more gradual but also more chronic course The characteristic findings are evidences of increased blood hemolysis as shown by increased indirect reacting serum bilirubin increased reticulated erythrocyte count as evidence of increased blood formation hyperplastic marrow increased fecal excretion of urobilinogen and commonly splenomegaly of varying degree Practically all cases of hemolytic anemia secondary to sulfonamide drugs have occurred during the febrile course of the illness for which the sulfonamide was given Withdrawal of *the drug results in improvement* although *transfusions* may be necessary

Leukemia like reactions can be caused by drugs Aminopyrine *arsphenamine benzene quinine and sulfonamides may* cause leukemoid reactions and benzene can cause leukemia

Hair dyeing solutions have caused some cases of macrocytic anemia thrombocytopenia and varying *leukopenia*

Of all the blood dyscrasias caused by drugs aplastic or hypoplastic anemia has the highest mortality Since the period between administration of the drug and onset of symptoms or changes in the blood picture is frequently long and since the reaction is rarely acute there is as yet no means whereby the physician can recognize indications for withdrawal of the drug and thus prevent the development of the bone marrow changes The symptoms may be of the anemia or the purpuric manifestations as the result of thrombocytopenia *Chloramphenicol* has been the most recently discovered offender Many other drugs can cause this dyscrasia It is difficult to make a prognosis

[For further material on the mechanisms of drug induced agranulocytosis and purpura the reader may consult articles in appropriate chapters

in this section In the chapter on Other Anemias is additional information on the effects of chloramphenicol —Ed]

Acanthrocytosis Genetic Erythrocytic Malformation Karl Singer Ben Fisher and Meyer A Perlstein[3] (Michael Reese Hosp) describe the occurrence of a peculiar malformation of most of the circulating erythrocytes in a boy 13½ who had progressive ataxic neuropathy with involvement of the cerebel lum basal ganglions and dorsal columns and a history of a celiac syndrome in early childhood He was the offspring of



F g 41 —A th yt blood film (C t y f S g K *et* *l* Blood 7 577 591 J 195)

a consanguineous Jewish marriage Similar observations have been described in the literature in two siblings also of con sanguineous Jewish parents The latter patients had in addi tion retinitis pigmentosa

The erythrocytic anomaly consisted of an unusual type of crenation (Fig 41) The deformed red cells showed several irregularly spaced large coarse projections on their surface which varied in width and length Many of the cells resembled spherocytes with pseudopods The term acanthrocyte (thorny red cell) is proposed for this type of red cell

(3) Blood 577 591 J 195

The acanthrocytes exhibited slightly decreased osmotic markedly increased lysolecithin and mechanical fragility but a normal heat and acid fragility However there was no significant anemia Hemoglobin pigment appeared normal The hemolytic index was within normal range precluding an exaggerated hemolytic process in vivo

It is suggested that acanthrocytosis is genetically conditioned and due to a mutant recessive allele for a gene which controls the normal architecture of the red cell Further observations are required to establish whether the association of acanthrocytosis celiac disea e in early childhood and ataxic neuropathy with or without retinitis pigmentosa constitutes a new hereditary syndrome

[Although of no hematologic significance clinically other cases may be discovered if the abnormality of the red cells is *noted on routine* blood examination —Ed]

Bone Marrow Aspiration Posterior Iliac Crest, an Additional Safe Site is described by Howard R Bierman[4] (Univ of California) The surface of the posterior iliac crest is particularly broad The bone usually approaches the surface and the ma s of bone marrow in this region is large and safely distant from important structures

Technic —With the patient prone on a hard flat surface the regions of both posterior iliac crests are aseptically prepared The most accessible site is selected from the posterior inferior or superior iliac spine anteriorly and the skin periosteum and intervening tissue are anesthetized by procaine infiltration The aspiration needle is pointed anterolaterally in the direction of the iliac crest The rest of the procedure is the same as at other sites

Such aspirations have been done without difficulty in 50 children and adults The prone position facilitates restraint of children and obviates the anxiety engendered by observing the preparations for the procedure

The author suggests that metastases from deep pelvic neoplasms may be picked up oftener at the posterior iliac crest than elsewhere because of its proximity to the direct vascular flow from the deep structures The site appears to be satisfactorily representative of the general character of the bone marrow

Superiority of Iliac over Sternal Marrow Aspiration in Recovery of Neoplastic Cells is discussed by Michael A Rubinstein and Amiel Smelin[5] (Montefiore Hosp New York City)

(4) C l for a Med 77 138-139 Augu t 1952
(5) A M A A ch Int Med. 89 909 913 J 195

who studied 100 consecutive patients hospitalized for advanced metastatic disease In each patient sternal and iliac marrows were simultaneously aspirated In smear preparations tumor cells generally appeared in clumps along the edges of the smear especially if the hemopoietic elements of the marrow were reduced Sometimes only tumor tissue was aspirated

Malignant cells were found in 41% of the patients Sternal and iliac marrows were normal in 59 patients and positive in 15 Iliac marrow was positive in 22 patients whose sternal marrow was normal Sternal marrow was positive in four patients with negative iliac smears they had thoracic neo plasms

Positive aspirations were commoner in patients with roent gen evidence of bony metastases than in those without Six patients without roentgen evidence of bone involvement had positive iliac aspirates one had a concomitant positive sternal aspiration

The high yield of malignant cells on aspiration was attributed to the fact that most of the patients were in the late stages of metastatic disease

The iliac marrow excels the sternal marrow as a site for the aspiration of tumor cells When marrow aspiration is part of the diagnostic work up or is used in an obscure syndrome or in one suggestive of cancer or to demonstrate metastatic bone involvement the procedure of choice is iliac rather than sternal puncture

Splenic Puncture is described by Jyoti B Chatterjea (Rockefeller Found) Carlos Meza Arrau (Univ of Chile) and William Dameshek[6] (Tufts College)

TECHNIC —The patient is given nothing by mouth for at least two hours before puncture He lies supine on the left side of the bed and the operator stands at his left The spleen is palpated its lower border outlined and the proposed site of puncture located usually in the left upper quadrant slightly below the costal arch Only readily palpable spleens have so far been punctured

The skin overlying the spleen i aseptically prepared and the previously defined skin area is anesthetized with 2% procaine hydro chloride infiltration using a 25 gauge needle Local infiltration is continued to the peritoneal layer with a 20 gauge needle The patient is then instructed to take a few preliminary inspirations care being taken to see that he can hold his breath at the height of inspiration He is instructed in what is to take place and on the need to hold his breath Proper co operation on this point is essential since punc

(6) B t M J 1 987 990 M y 10 1952

ture is always made at the end of inspiration with the patient holding his breath Splenic puncture is contraindicated for unconscious or un co-operative patients A dry 10 ml sterile syringe with an attached 20 gauge needle (6 8 cm long) is used The needle is quickly pushed through the skin and subcutaneous tissue to the abdominal muscle during normal breathing While the breath is held in full inspiration the needle is quickly pushed through the muscle and peritoneum into the splenic substance a quick strong aspiration is made and syringe and needle are immediately withdrawn Maintenance of negative pressure during withdrawal of the needle is optional

After withdrawal of the needle gentle pressure with a gauze pad is applied to the puncture site After a few minutes the area is dressed with several more gauze pad and adhesive tape The patient lie in bed for two hours during which nothing is given by mouth Preferably he would remain in bed for at least six hours splenic punctures have however been done on out patients who were sent home to bed after two hours of observation

The amount of aspirate is scanty a few drops at most The aspirate is gently ejected on clean glass slides smears are immediately made in the usual fashion They are treated with combined Wright and Giemsa stain No fixed section method is used The smear i first examined under low power for foreign cells megakaryocytes or abnormal cellular clumps Often the serosa or mesothelial cell derived from the peritoneum of the spleen is seen u ually in sheets or clumps Under oil immersion 500 nucleated cell are counted

Splenic puncture is contraindicated when severe hemorrhagic manifestations exist and when the spleen is apt to rupture as in recent septic splenomegaly in infectious mononucleosis and acute malarial spleen and in painful or tender spleens suggestive of recent splenic infarction

In idiopathic myelosclerosis and myeloid metaplasia the splenogram shows diminished but active lymphopoiesis many erythroblasts immature granulo and megakaryocytes The splenogram in granulocytic leukemia reveals greatly diminished lymphopoiesis and numerous granulocytic elements in different stages of development In lymphocytic leukemia and lymphosarcoma lymphocytic elements increase Monocytes reticulum cells and granulocytes are increased in reticulum cell sarcoma In polycythemia vera the splenogram shows ectopic hemopoiesis with all the elements of normal bone marrow In hemolytic anemia there is a slight increase in neutrophils and a small number of erythroblasts Hypersplenic pancytopenia and cirrhosis of the liver show dilute hypocel

lular smears In Gaucher s disease characteristic lipid laden cells are present In sarcoidosis no specific cytologic pattern was evident

Splenic puncture is indispensable in the diagnosis of myeloid metaplasia The association of a fibrotic or sclerotic bone marrow with extensive myeloid metaplasia of the spleen is an absolute contraindication to splenectomy [Probably not so if substantial evidence for increased red cell destruction exists See chapter on Hypersplenism —Ed]

Splenic puncture is most useful in the diagnosis of atypical or cryptic types of aleukemic leukemia and leukosarcoma where the marrow picture may not be diagnostic or may even be normal This is particularly true in primary lymphosarcoma and in reticulum cell sarcoma of the spleen in which splenomegaly may be the only abnormal finding

Adrenalin® (Epinephrine) Test as Applied to Hematologic Disorders Jyoti B Chatterjea William Dameshek and Mario Stefanini[7] (Tufts College) performed the epinephrine test in 12 normal subjects and 63 patients with various hematologic disorders to evaluate its role in the diagnosis of hypersplenic syndromes and aplastic anemias Attention was directed solely to the early phases of the reaction that is to the preadrenocortical stimulatory effect which has been claimed to reflect the functional activity of the spleen and bone marrow The response in normal subjects was characterized by transitory pancytosis Leukocytosis and thrombocytosis were conspicuous whereas erythrocytosis and reticulocytosis were not regularly seen Leukocytosis was due to an increase of mature forms of neutrophils lymphocytes monocytes and eosinophils The Arneth count did not show any significant variation after epinephrine There was no correlation between the degree of hemopoietic response and degree of rise of blood pressure although in each case the time of maximal cellular response usually ran parallel to the time of maximal rise of blood pressure

The response in splenectomized patients was essentially similar to or slightly greater than that in normal subjects In splenomegalic conditions there was no correlation between degree of splenic contraction and degree of hemopoietic response Results of injection of epinephrine into the splenic artery showed that the increase of cellular elements was pan

(7) Blood 8 11 235 M h 1953

cellular in type and not confined to any particular cell deficient in the peripheral blood it was obviously independent of the nature and degree of peripheral cytopenia Splenic contraction following epinephrine may be due to severe constriction of the splenic artery and its intrasplenic branches with resultant passive deflation of the organ In each case there was a close correlation between the response to epinephrine and the functional activity of the bone marrow

The epinephrine test per se is not diagnostic of any clinical condition In the hypersplenic syndromes interpretation of negative results may actually be misleading At most the test provides indirect corroborative evidence of the functional status of the blood forming tissues and to some extent of the reservoir of blood cells present not only in the bone marrow but in various tissues and organs throughout the body The exact degree of splenic participation in the epinephrine response is not known but studies indicate that it is minimal

Effect of Blood Coagulation on L E Cell Formation is studied by Frederick L Zimmer and Malcolm M Hargraves[8] who treat coagulation as a potentiating agent Nucleolysis produced by some specific lytic agent seems the fundamental mechanism in formation of L E cells Their production depends on lytic factor contained in an antigenic fraction of the gamma globulin nuclear protein to react with the lytic factor and viable phagocytic leukocytes Methods demonstrating L E cells attempt concentration of these factors in the presence of anticoagulants or in defibrinated plasma The in vitro nature of the process suggested a relationship between clotting and L E cell production A method was devised to bring the three factors together during coagulation

TECHNIC—Five or 10 cc of a patient s venous blood is drawn and allowed to coagulate at room temperature for 60 120 minutes The clot is then fragmented with wooden applicator sticks and removed from the now bloody serum The serum cellular mixture is centrifuged for five minutes at 2 000 r p m and 1 cc of the top layer of cells is transferred to a Wintrobe hematocrit tube for a similar period of centrifugation The concentrated leukocytic layer is removed smeared on glass slides stained with Wright s stain and examined under oil immersion Leukocytes are found in greatest number along the sides and feathered edge of the smear

L E cells were found in much greater numbers when the leukocytes were in contact with the L E factor during coagu

(8) Proc. Staff Meet. Mayo Clin 27 424-430 Oct. 22 1952

lation than when they were not suggesting enhancement by some substance active during blood clotting [Possibly fibrin strand formation aids mechanically in phagocytosis as shown by Ward s studies with phagocytosis of bacteria —Ed]

Blood of 125 patients chosen at random or because of clinical suspicion of collagen disease was tested by this two hour blood clot technic Clinical diagnosis in six cases was acute lupus erythematosus in all the blood clot test gave a positive result whereas the result of bone marrow examination was positive in four of five cases so tested Chronic or subacute systemic lupus erythematosus was present in 15 patients blood clot examination gave positive results in 12 whereas marrow examination gave positive results in only 1 of 12 examined marrows In 7 of 11 patients examined before establishment of a diagnosis clot examinations gave positive results whereas none of 8 marrows examined showed the L E cell phenomenon

Monocytic histiocytic or polymorphonuclear tart cells may be mistaken for L E cells The secondary nucleus of a polymorphonuclear tart cell is likely to show pyknotic changes dense staining a heavy border and angular fenestrations Erythrophagocytosis and abnormal appearing basophils may also cause confusion in the two hour blood clot technic

L E cell formation is potentiated by blood coagulation The technic is more sensitive than others using peripheral blood or heparinized marrow

Demonstration of L E Phenomenon in Patients with Penicillin Hypersensitivity John R Walsh and Hyman J Zimmerman[9] (Omaha) found L E cells in concentrated heparinized marrow preparations from three patients with severe penicillin reactions but not in marrow preparations from three with mild urticarial penicillin reactions

Demonstration of the L E phenomenon in patients with penicillin reactions may have one of a number of implications that the test is nonspecific for systemic lupus erythematosus and may be positive in unrelated conditions that penicillin reactions produce pathologic and serologic changes related to systemic lupus erythematosus that the L E phenomenon may be related to hypersensitivity without the histologic changes of systemic lupus erythematosus or that there is coincidental lupus erythematosus

(9) Bl od 8 65 71 J y 1953

There has been an increasing amount of recorded data supporting the reliability and specificity of the L E phenomenon for systemic lupus erythematosus In view of the demonstration of a high degree of specificity for this phenomenon its occurrence in severe penicillin hypersensitivity suggests a relationship to systemic lupus erythematosus Severe penicillin reactions may show many similarities to serum sickness The histologic changes in such cases are similar to those seen in



Fig 4 —L E c ll (Cou t y f W l h J R nd Z mm ma H J Blood 8 65 71 J y 1953)

serum sickness Such observations are in keeping with those of Klinge and his associates and of Rich showing the interrelationship of the group of diseases called the collagen diseases and their association with the hypersensitivity state Since lupus erythematosus is a collagen disease related to the hypersensitivity state and since penicillin reactions have been shown to be capable of producing hyperergic vascular and connective tissue changes it seems possible that a penicillin reaction may produce lupus erythematosus

The possibility that the L E phenomenon occurs in hypersensitivity states and is not necessarily related to histologic changes of the collagen diseases cannot be evaluated from available data

Lupus erythematosus may have been present in one of the patients Clinically it is extremely unlikely that it was present in the other two

[Stuart Finch has recently produced cells closely resembling the L E cell by in vitro incubation of normal human granulocytes in rabbit anti serum developed against these cells This is consistent with a s nsitivity phenomenon in the clinical situation —Ed]

Nonwettable Surfaces James L Tullis and Eugene G Rochow[1] state that the importance of u ing nonwetting sur faces for in vitro handling of blood is generally accepted With the use of untreated glass there is platelet disintegration with consequent activation of the clotting mechanism and severe damage to leuk ocytes consisting of decrease in ameboid motility phagocytic index and respiration Red blood cells are not harmed by wettable surfaces Glass is easily rendered nonwettable by treatment with methyl chlorosilane or liquid silicone Metal can be made nonwettable by application of Arquad 2 C Teflon or the silicone resin lacquers

Silicone is deposited on glass from the reaction between methyl chlorosilane and the thin film of water vapor on the surface of the glass Liquid silicone (Dri Film 9987) is applied by actual immersion of the surface to be siliconed followed by rinsing to complete the hydrolysis and the removal of hydrochloric acid This method has been superseded by the vapor silicone process due to its ease of application The vapor treating material (Dri Film 9977) lends itself readily to the siliconization of large amounts of equipment in minimal time

Method —All glassware must be properly washed with soap and water 24 hours before application After wa hing t e glassware is thoroughly rin ed in warm tap water followed by hot pyrogen free distilled water It is placed in a hot air oven and dried for two hours at 120 C and then allowed to stand overnight at room tem perature in order o bring it to equilibrium with the moi ture in the atmosphere ince the vapor will not adhere to a completely dry surface The glassware is put in containers and placed under a chemical hood About 20 cc Dri Film 9977 is placed in a gas washing bottle and air is bubbled slowly through it The resultant vapor i directed through a rubber tube and glass nozzle into each of the containers of glassware The tube should be held in each container only long enough for the operator to count slowly to six The gas bottle is disconn cted and a stream of compres ed air is directed into each container for the same period in order to di place the extra methyl chlorosilane vapor The glassware is removed and aft r it is rin ed three times with hot pyrogen free di tilled water

(1) Blood 850 853 A gu t 195

to free it from hydrochloric acid it is ready for immediate use or sterilization

It is best to remove the silicone layer after each use to insure protection against pyrogens and other contaminants Removal is accomplished by exposing the glassware to 10% *sodium hydroxide* solution for at least two hours followed by thorough washing and rinsing

Arquad (dicoco dimethyl ammonium chloride) is used for the application of nonwettable surfaces to needles and other stainless steel parts Needles are prepared by *routine* cleaning methods and then boiled in a 1% solution of Arquad for two minutes They are then rinsed dried and used The surface should be applied after each use

Dri Bake and Pan Glaze are lacquer silicones used to siliconize stainless steel apparatus The materials to be treated are brushed or dipped into the resin solution and allowed to drain and dry They are then baked in an oven at 230 C for three hours After 150 or more exposures to blood the previous coating can be removed by strong alkali

Teflon can be used as a solid nonwettable plastic from which test tubes and other parts can be machined or it can be used as a powder which is sprayed over a metal surface to form a semipermanent coating

Importance of Blood Groups in Laboratory and Clinical Medicine Fred H Allen Jr[2] (Harvard Med School) lists nine important blood groups including A B O Rh M N S Kell Duffy Kidd P Lewis and Lutheran of which the Rh system is the largest and most complicated Blood groups important in blood transfusion and in pregnancy are A B Rh (D C c E e) M N S s K k Fy^a Fy^b and Jk In at least 95% of clinical difficulties resulting directly from blood groups A B or Rh (D) are involved Blood groups which rarely if ever cause transfusion reactions or erythroblastosis fetalis are O P Le^a Le^b and Lu^a Blood groups are important in legal medicine for identification of persons and the exclusion of paternity They are also of great value in physical anthropology and in the study of human genetics in which at least eight different chromosomes are tagged by blood group genes

Presumably A and B are the strongest antigens and therefore the most important ones in blood transfusions in which there can be no leeway for errors in typing or cross matching

(2) New Engl J Med 47 379 383 Sept 11 1952

The first error results in hemolytic reactions that may be fatal Next comes the Rh factor (D) also an effective antigen which usually sensitizes the negative person who is exposed to it through a blood transfusion Sensitization in itself has no harmful effect on the person sensitized but a second such transfusion causes a hemolytic reaction which may be fatal Sensitization may also occur in an Rh negative mother to an Rh positive fetus Many K negative persons can be sensitized to K (Kell) by transfusion of K positive blood the same is true of E and c but none of these is as important as A B and D Fatal transfusion reactions due to A B or D can be avoided by accurate blood typing tests Fatal reactions due to K E c and the others are so uncommon that routine typing for these factors is not warranted

Over 80% of transfusions are potentially dangerous be cause of the possibility of sensitizing the recipient to E c Kell Duffy S or one of the other antigenic blood factors Husbands are undesirable donors for their wives if other donors are available Hemolytic transfusion reactions can be avoided by use of the Coombs test for the cross match

Effective treatment of erythroblastosis fetalis requires prepartum testing of pregnant women observation of jaundice in all newborn babies and close co operation among obstetri cian pediatrician nursing staff and blood bank Kernicterus which is the principal complication of erythroblastosis fetalis and which used to claim 15% of erythroblastotic infants can be prevented by proper treatment It is necessary to know if the pregnant woman is D negative and if so whether she has been sensitized to D Blood typing and the sensitization test can be done at about seven months gestation If no anti Rh antibodies are found at seven months the test should be repeated three or four weeks from term If sensitization to D is detected erythroblastosis should be expected and complete preparation should be made regardless of the maternal titer Preparation means immediate exchange transfusion with Rh negative compatible blood Nothing can be done before the birth of the infant

When the babies are born they are not jaundiced Jaundice the most important clinical feature almost invariably appears within 24 hours of birth except in the 15 20% of erythroblastotic babies who never have trouble of any kind The severity of jaundice is directly related to the likelihood of

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(2) New Eng J J Med 47 379 383 Sept 11 1952

dextrose to determine post transfusion survival after storage at 4 C for periods up to 29 days These 37 donations were a representative sample of 442 blood specimens infused into patients All the blood donations were collected stored and infused with plastic equipment Data obtained by in vivo survival studies in 12 experiments and in vitro measurements in 25 experiments demonstrated that 70 80% of the cells of blood stored up to 25 days retain normal functional capacity after infusion The condition of preservation of these blood specimens was such that 88 92% survival can routinely be expected up to 10 days 84 88% up to 14 days 76 84% up to 20 days and 70 80% up to 25 days of storage at 4 C

In vivo post transfusion survival of red cells was determined by a modification of the differential agglutination technic of Young This technic demonstrates that cells which irreversibly deteriorate during storage are rapidly removed from circulation and the functional integrity of the remaining cells is shown by their normal disappearance rate In vitro post transfusion survival of red cells was determined by measuring the osmotic fragility of the cells This is based on measurements of the percentage of hemolysis of blood in different concentrations of sodium chloride There is a fair correlation between osmotic resistance characteristics and in vivo survival of red cells

Pathogenesis of Plasma Transfusion Reaction with Especial Reference to the Blood Coagulation System is discussed by William H Crosby and Mario Stefanini[4] (Boston) Dameshek and Neber described a reaction occurring in susceptible patients during transfusion of compatible whole blood consisting of chill fever backache leg pain cyanosis and hyperperistalsis without sign of allergy or sudden intravascular hemolysis Red cells could be washed free of the provoking plasma factor and transfused safely This factor is destroyed by heating at 56 C for 30 minutes The plasma transfusion reaction (PTR) has been encountered in patients with acquired hemolytic anemia severe pernicious anemia sickle cell anemia leukemia and in patients with aplastic anemia and terminal cancer usually after many previous transfusions Although PTR is rare in these conditions it is the rule in paroxysmal nocturnal hemoglobinuria Here the reaction is similar to that

(4) J Lab & Cl M d 40 374 386 S pt mbe 1952

brain damage Exchange transfusions can lessen the severity of the jaundice and thereby prevent brain damage

Erythroblastosis is a disease caused by fetal maternal blood group incompatibility the baby having a blood factor that its mother lacks the mother producing antibodies (against that factor) that pass through the placenta into the baby s circulation the baby s red cells are rapidly destroyed after contact with the antibodies At birth the infant has severe anemia and is unable to excrete bilirubin which rapidly accumulates Exchange transfusions replace the infant s red cells with red cells compatible with the maternal antibody thereby greatly reducing the formation and concentration of bilirubin A second exchange transfusion should be done to prevent the bilirubin *from rising above 20 mg /100 cc*

Diagnosis of erythroblastosis fetalis depends on what blood factor is causing the trouble in the particular case In perhaps 80% of cases it is the Rh factor (D) The mother is Rh negative and a positive Coombs test result in the infant confirms diagnosis of erythroblastosis In the other 20% the mother is usually Rh positive If the mother is Rh positive and the result of the Coombs test of the baby s red cells is positive the diagnosis is erythroblastosis of one of the uncommon groups caused probably by Kell L or c If however the result of the Coombs test is negative and the baby is *incompatible with the mother in the major blood groups* it is almost certain that it is one of that fairly large group of cases caused by major blood group incompatibility This type of erythroblastosis is generally not predictable before birth In these cases the baby s serum bilirubin rises to 15 mg */100 cc* or higher within 24 hours of birth and the mother s serum almost invariably has a very high titer of hyperimmune anti A (or anti B) antibody Erythroblastosis caused by A B O incompatibility although usually mild should be treated by exchange transfusions if necessary to keep the serum bilirubin below 20 mg /100 cc

[*In fact* for many oth r r asons as well the physician should always ask himself Is this transfusi n really n cessary? —Ed]

Preservation of Whole ACD Blood Collected, Stored and Transfused in Plastic Equipment Theodore Sack John G Gibson 2nd and Edward S Buckley Jr[3] (Harvard Med School) studied 37 blood donations preserved in acid citrate

(3) Su g Gynec & Ob t 95 113 119 July 195

ACTH was given intramuscularly every six hours for a usual course of 1 Gm in 10 days Children under 16 received about 40 mg daily for 10 12 days Oral and intramuscular doses of cortisone ranged from 1 5 Gm in 10 days to 3 5 Gm in 30 days Blood transfusion was used when necessary

Good response implies obvious clinical improvement plus decisive changes in relevant laboratory findings Partial re sponse implies either measurable clinical improvement or some improvement in laboratory data The panel s experience coin cides with other recent series (see table) It is concluded that

RESPONSES TO ACTH AND CORTISONE IN BLOOD DISORDERS

			Re s			
			Good		P ti l	
	C s s	N	I	P†	I	P†
H molyti an mi	19					
A q d	(11)	3		3	3	2
Cong tal	(6)	6				
Noct. hem gl b emia	( )	2				
P rp	14					
Idi p th th ombocyt penia	(10)	5	1	1	1	
Toxi	(4)	1			1	
Le k m	40					
Acut d submy l d	(16)	12		1	3	
Lymphati						
A t	(12)	7			4	1
Ch	(1)	1				
A t m ocyt	(5)	5				
Ln l h d	(3)	3				
My l m t	(2)	2				
R t l sa coma	(1)	1				
M ll eo	15					
Apl n m	(2)	2				
R f ct ry w th ct ma w	(5)	5				
My l l	(5)	4				
P h mat pen a	(3)	3			1	
T t l	83	62	1	7	15	3

I = mmediat m g d g t tm t ly
†P = p l g d m g ma t d at lea t m th fter t tm t w stopped

as presently used these hormones are unlikely to be important in treatment of blood disorders Best results are obtained in acquired hemolytic anemia and thrombocytopenic purpura in which uncertain unpredictable and sometimes short remission can be promoted Hemolytic components of aplastic and refractory anemias may be benefited In acute leukemia in children life may be increased a few weeks to months

The usual side effects and no fatalities were attributed to therapy with ACTH and cortisone

[The value of these agents in the control of acquired hemolytic anemia and in th ombocytopenic pu pura e pecially as preparations for splenec ton y is documented in the chapters that follow —Ed.]

in the other anemias but invariably is followed by hemolytic crises some hours later

The plasma factor which destroys abnormal red blood cells in nocturnal hemoglobinuria resembles but is not identical with accelerator globulin A rapport exists between coagulation and the hemolytic system in nocturnal hemoglobinuria suggesting that PTR hemolytic in nocturnal hemoglobinuria might involve the coagulation system The behavior of various clotting factors was investigated during PTR which can reliably be produced in nocturnal hemoglobinuria PTR was induced in three such patients

At the time of the chill the blood became hypercoagulable although platelet count prothrombin activity and fibrinogen concentration were at the same time much reduced suggesting that a generalized attempt at intravascular coagulation occurred during this phase Thereafter intense fibrinolytic *activity rapidly developed in the plasma* An unidentified anticoagulant activity appeared

The symptoms of PTR *may* be *due to* embolism In the preliminary phase most of the leukocytes and platelets are swept out of the circulation and about half of the fibrinogen disappears The *white* cells are probably *removed by* the lungs Platelet or fibrin emboli may cause such clinical symptoms as diarrhea headache and abdominal pain Small emboli by injuring the bone marrow may be responsible for the shower of reticulocytes and nucleated red cells associated with PTR Similar reaction in the lung may explain the fibrinolytic activity in the plasma

The plasma transfusion reaction is *nonspecific* since the same pattern of changes occurs in a variety of other conditions for example following the injection of peptone or killed typhoid bacilli

Treatment of Blood Disorders with ACTH and Cortisone Preliminary Report to Medical Research Council by the Panel on Haematological Applications of *ACTH* and *Cortisone*[5] (L J Witts C J C Britton L S P Davidson L J Davis A Haddow, Lionel Whitby J F Wilkinson and P L Mollison) is based on 88 patients treated without controls during the *first year* of evaluation of these hormones

(5) Brit M J 4771 1261 1263 Jun 14 1952

react at 4 C are cold agglutinins In acquired hemolytic anemia cold agglutinins are present in higher titer than in normal persons Antibody titer and severity of the disease are not definitely correlated

Some patients have a relatively benign prognosis and respond to conservative treatment Three patients treated with transfusions and 100-200 mg cortisone daily went into remission in 7 14 days The prognosis for patients with cold hemagglutinins is better than for those with warm hemagglutinins Splenectomy is the treatment for patients who do not respond to conservative therapy The choice is based on two hypotheses (1) removal of an organ largely responsible for erythrocyte destruction and (2) removal of an important source of antibody formation Cortisone corticotrophin or both have been used often Two patients responded to cortisone and six others improved but had to undergo subsequent splenectomy when it became obvious that remission could be maintained only by continuous cortisone therapy The use of cortisone made the operation safe and five patients were maintained on cortisone after surgery Use of cortisone corticotrophin or both has greatly improved the outlook for patients with this disease

Hemolytic Anemia Presumably Due to Coexistence of Genes for Thalassemia and Sickling John S Lawrence James V Neel and Harvey A Itano[7] (Los Angeles) report a case of sickle cell anemia in a woman 35 of Greek extraction One parent had sickle cell trait and the other thalassemia minor Two brothers had thalassemia minor one sister had sickle cell trait and one brother had sickle cell disease presumably due to the same heterozygosity as the patient

There is no doubt that most cases of sickle cell disease unlike the one reported develop on the genetic background of homozygosity for the gene responsible for sickling

The second most frequent type of sickle cell disease appears to be that which develops in a child receiving the gene responsible for sickling from one parent and the gene responsible for a new and poorly understood hemoglobin abnormality from the other This new hemoglobin has been designated hemoglobin III or hemoglobin c It seems to be due to a dominant gene On the basis of preliminary figures it

(7) T A Am Phy 65 03 13 1952

Diagnosis and Treatment of Acquired Hemolytic Anemia is discussed by Milton S Sacks Joseph B Workman and Elsa F Jahn[6] (*Univ of Maryland*) on the basis of *19* personal patients and an analysis of 147 cases from the literature of 1940 51 In vitro and in vivo immunologic studies have proved that the basic pathologic physiology of acquired hemolytic anemia consists of an accelerated destruction of erythrocytes presumably due to an autoagglutinin which is firmly attached to the red blood cells and is capable of reacting with any normal human erythrocytes Its cause is unknown The disease may appear in previously healthy persons (idiopathic acquired hemolytic anemia) or it may develop in patients with primary atypical pneumonia with one of the lymphomas or with one of the collagen diseases (symptomatic acquired hemolytic anemia) It can occur at any age but is more prevalent among females

Diagnosis is based on the absence of familial hemolytic disease a negative history of exposure to known hemolytic agents and characteristic immunologic findings Onset and course may vary The patient may be acutely ill with fever jaundice and splenomegaly and may show pallor hemoglobinuria and tachycardia The blood picture is that of normocytic anemia with normal or slightly elevated leukocyte count and a normal number of platelets there is spherocytosis reticulocytosis and normoblastosis the indirect plasma bilirubin level is elevated urobilinogen excretion in the urine and feces is increased and there may be a false positive syphilis reaction

The most constant immunologic finding is a positive agglutination reaction to anti human globulin serum (Coombs test) The patient s serum usually contains a panagglutinin which can react with any normal human group O red blood cells and may first be noted in the performance of a routine red cell count To demonstrate it agglutination tests at various temperatures and in several mediums are necessary Results of the Coombs test in all 19 patients were positive Sixteen patients had panagglutinins or autoagglutinins which reacted at 22 and 37 C They are called warm agglutinins Those which

(6) J.A M A 150 1556-1559 Dec 20 1952

rapid method of mixing a drop of blood with a drop of 2% sodium bisulfite solution and superimposing a cover slip This parent s blood on electrophoretic analysis failed to exhibit the pattern characteristic of sickle cell trait hemoglobin The hematologic findings were consistent with those commonly



F g 43—M t p p t n f blood f boy wh m th h thala sem m no Spec m n h ws yth cytes n o tag f kl g All l al d l bo tory find w comp t bl w th d g f kl ll m (Court y f L nk L O t l A M A Am J D Ch ld 84 601 608 N er be 195)

seen in persons with thalassemia minor Observation in this case as well as the reports of other workers indicates that the mating of a person carrying the sickling trait with another person bearing the thalassemia trait can result in a disease in the offspring indistinguishable from sickle cell anemia (Fig 43)

Hyperhemolysis of Nonsplenic Origin in two patients is discussed by Olle Hogeman[9] (Univ of Uppsala)

(9) A ta m d d 144 47 6 19 3

appears that in 6% of the Negro families studied in which sickle cell disease was present the disease was due to the combination of a sickling gene with one responsible for the new hemoglobin abnormality In the Detroit Negro population approximately 3 of 1 000 persons should be heterozygous for the latter gene Persons who are homozygous for the gene would be expected to occur with a frequency of about 2 5/1 000 000 births No such persons have been recognized to date This type of sickle cell disease is milder than the more usual variety

The third most common type of sickle cell disease is that due to the coexistence of the genes for sickling and thalassemia This type probably accounts for most cases of sickle cell disease described in presumably Caucasian persons It is more than coincidence that so many of these cases in Caucasians occur in people of Greek or Italian derivation

Finally what appears to be a fourth type of sickle cell disease has recently been described in an apparently Caucasian child It seems to be due to interaction of a sickling gene with a previously undescribed gene which is also responsible for a hemoglobin abnormality This type of hemoglobin has the electrophoretic mobility of sickle cell type hemoglobin but is not associated with sickling

[The original article has numerous tables and diagrams which are helpful in understanding the various genetic relationships —Ed]

Studies in Sickle Cell Anemia Inheritance Factor, Including Effect of Interaction of Genes for Sicklemia and Thalassemia L Otto Banks Roland B Scott and Juliette Simmons[9] (Howard Univ) studied the families of 16 patients with sickle cell anemia Of the 25 parents tested 24 showed the sickling trait For several multiple examinations were necessary before in vitro sickling could be demonstrated Of the 57 offspring in the 16 families 18 had sickle cell disease 15 had sickle cell trait 18 were normal and 6 were not tested The finding with one exception were compatible with the genetic hypothesis advanced by Neel and Beet for the inheritance of sickling i e that the asymptomatic sickle cell trait occurs in those heterozygous for the sickling gene and sickle cell disease occurs in those who are homozygous

The blood of the mother of one patient failed to sickle on repeated testing with various methods including the usually

(9) A M A Am J D s Child 84 601 608 N emb r 1952

in the spleen and (2) the production of anti red cell immune bodies in the reticuloendothelial system

These theories explain hemolysis in both cases studied In Kaposi s disease a deplasmatization with accompanying hemolysis may have taken place in the enormously expanded angiosarcomatous tissue which would then act as a vicarious spleen (according to Fahraeus and Bergenhem s theory on splenic function)

Hypersplenism must be distinguished from hyperhemolysis Hypersplenism implies an increase of the normal inhibitory action of the spleen on the marrow with resulting leukopenia thrombocytopenia and anemia Anemia would then be caused by a release by the marrow of fewer red cells and by destruction in the spleen of more red cells than is normal The second patient s anemia did not disappear after splenectomy the usual treatment for hypersplenism The mechanism of hemolysis continued to exist in the enormously expanded Kaposi sarcomas of the skin stomach liver and glands Whether hyperhemolysis will disappear after splenectomy depends entirely on the pathologic process that causes splenic enlargement If only the spleen is affected hyperhemolysis will cease if not there is compensation in other parts of the reticuloendothelial system and eventual recurrence

In Vitro Erythrophagocytosis in Acquired Hemolytic Anemia. It has been found that marked erythrophagocytosis occurs when the buffy coats of patients with this disease are incubated in vitro In a control series of 95 normal adults studied by William H Zinkham and Louis K Diamond[1] (Harvard Med School) the erythrophagocytic index of the incubated buffy coat (percentage of erythrophagocytic cells in 500 phagocytic leukocytes counted) was never greater than 0 1% whereas in 3 of 4 patients with acquired hemolytic anemia indexes of 5 80% were observed All four patients had abnormalities of serum and red cells as demonstrated by direct and indirect Coombs tests trypsinized red cell test and increased mechanical fragility of incubated red cells Only three however showed in vitro erythrophagocytosis (Figs 44 and 45)

The in vitro method consists of incubating heparinized or oxalated venous blood at room temperature for ½ hour and then centrifuging it at 2000 rpm for 10 minutes The buffy

(1) Blood 7 59 601 J 195

CASE 1 —Woman 34 had for two years had increasing pain in the bones Severe anemia which increased despite repeated blood transfusions was discovered She had bilirubinemia and reticulocytosis the spleen was only slightly enlarged Results of the hypotonic fragility test were normal once and slightly reduced another time but this did not explain the colossal hemolysis No pathologic agglutinins were found After death carcinoma of the stomach with metastasis to the lymph nodes was discovered The hemolysis must have been occasioned by extracorpuscular factors

CASE 2 —Man 48 who had previously been in good health was hospitalized for acute gastric hemorrhage traced to generalized Kaposi s disease Cutaneous manifestations had initially been so slight that he had hardly been aware of them Because of persistent anemia leukopenia thrombocytopenia reticulocytosis reduced survival of red cells and splenic enlargement Kaposi s sarcoma of the spleen with concomitant hypersplenism was suspected After splenectomy his condition deteriorated appreciably the blood counts fell and the angiomatous process advanced rapidly The survival of red cells postoperatively was shorter than before Further deterioration was rapid and he died in advanced cachexia and icterus with large swellings probably attributable to severe hypoalbuminemia

Although the spleen plays an important part in producing hemolysis in conjunction with various conditions hemolysis can occur without any apparent splenic engagement In the cases reviewed hemolysis developed although the spleen was uninvolved The entire reticuloendothelial system of which the spleen is part is concerned in hemolysis Both patients had extensive infiltration in other reticuloendothelial organs the liver glands and marrow Castle *et al* believe that red cell agglutination exists in acquired hemolytic anemia including that found in neoplastic disease At least under experimental conditions using anti red cell agglutinating serum agglutinins appear to start a chain reaction (1) agglutinated red cells appear in the peripheral blood (2) the red cells are sequestered and separated from the plasma in the tissue capillaries (3) then ischemic lesions of the tissue cells appear and release substances that locally increase the osmotic and mechanical fragility of the red cells and (4) local osmotic lysis results or mechanically fragile red cells enter into the circulation to be destroyed by continuous traumatization Red cell agglutinins have been found in abnormal spleens and tumorous tissue especially if necrotic will hemolyze red cells in vitro Doan believes the hemolytic mechanisms in such instances consist of (1) the physical collection and phagocytosis of red cells

peripheral phagocytes only during an acute episode when the fixed macrophage system is overloaded It is suggested that increased activity of fixed tissue macrophages and peripheral phagocytes toward altered red cells in certain diseases may explain mild degrees of anemia not associated with obvious signs of hemolysis

This method may be used as another in vitro technic for demonstrating abnormalities of the red blood cell

[Also the ear lobe of patients as opposed to the finger tip may yield smears showing erythrophagocytosi without incubation It occurs in hemolytic anemias in which a hemolytic mechani m is demonstrable in the test tube on an immunologic basis Besides hemolytic anemia erythrophagocyto is is very suggestive of subacute bacterial endocarditis—Ed.]

Hereditary Spherocytosis (Congenital Hemolytic Jaundice) Pathogenesis of 'Hemolytic' Crisis John D Battle Jr (Cleveland Clinic) reports observations on acute concurrent hemolytic crises in three brothers aged 12 7 and 6 with hereditary spherocytosis There was evidence of temporary marrow aplasia or maturation arrest reticulocytopenia and lack of icterus These findings support the current concept of Owren that transient marrow aplasia and not a sudden increase of hemolytic activity is the primary factor in the pathogenesis of the acute crisis Owren presented evidence based on a study of six members of one family with concurrent hemolytic crises including one studied just before onset During the crisis he noted reticulocytopenia leukopenia thrombopenia and in the marrow transient aplasia of erythropoiesis with maturation arrest of granulopoiesis

The cause of the crisis is not definitely known but there is considerable evidence pointing to an acute infection as the trigger factor All three brothers had an acute upper respiratory infection followed after an incubation period of eight days by the crisis This suggests a virus etiology

The initial blood studies during the crisis revealed profound anemia with a high percentage of microspherocytes reticulocytopenia and normal icterus indexes The mean red cell diameter was 6 μ The marrow obtained by iliac aspiration was hypocellular revealing a preponderance of granulocytic cells and a conspicuous decrease of late erythroblastic cells There were hypoplasia of the erythroid cells and maturation arrest of the proerythroblast stage (Fig 46) Several days after onset of the crisis the reticulocytes increased spontane

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coat is incubated for two hours at 37 C Smears are made at the end of the ½ hour at room temperature and at the end of 1 and 2 hours of incubation at 37 C

It has been shown that in vitro erythrophagocytosis occurs when red cells are damaged or altered by antibodies such as incompatible isoagglutinins or hemolysins such as the hemolysin of paroxysmal cold hemoglobinuria For example the red cells of fresh A B or AB buffy coats are promptly ingested by the surrounding leukocytes when fresh group O serum is added The factor or factors altering red cells in the patients studied



F g 44 (l ft) —D t m a of p phe al blood of p t nt w th a qu r d h m lyt c nem on day of dmiss on to ho p t l r du d fr m ×500
l g 45 (ght) —Sm f debbr nat d n u blood fte t d ng f e ho r t 37 C d e ons m d y a m r n F gu e 44 ed c d f m × 500 N te m y p lym ph n l n ut orh l yth ph g s nd l mp ng of d c ll around th s ell
(C rt y f Z kh rn W H and D m d L K Blood 7 59 601 J 195)

by the authors were not clearly defined Though all four had positive reactions to direct Coombs tests and increased mechanical fragility only three had in vitro erythrophagocytosis *However the degree of erythrophagocytosis seemed* related directly to the direct *Coombs* test titer

During erythrophagocytosis red cells clump about a phagocyte (neutrophil eosinophil or monocyte) which projects a pseudopod that sweeps the red cell into the cytoplasm of the white cell *This is repeated two to eight times* The ingested red cells lose structure and fade into the cytoplasm of the white cell which becomes immobile and eventually fragmented

The erythrophagocytic index of incubated buffy coat smears is greater than that of direct smears possibly because fragile erythrophagocytic cells are filtered rapidly by the liver spleen and lung It is also possible that damaged or altered red cells are removed by the stationary phagocytes of the reticuloendothelial system Altered red cells are available to

There is no uniformity of opinion regarding the management of the patients in acute crisis All three patients were treated with blood transfusions and two had splenectomies

[Singer and his associates (J Lab & Clin Med 35 721 736 May 1950) have observed similar aplastic crises in sickle cell anemia Indeed critical studies show that erythropoiesis is inhibited sometimes in normal persons with virus infection —Ed]

Acquired Hemolytic Anemia and Viremia Herbert R Morgan[3] (Rochester N Y) obtained whole blood specimens from six patients with acquired hemolytic anemia and specimens of spleen from three patients after splenectomy Hemolytic activity was evident in all but two of the patients when the specimens were taken Erythrocytes from six patients exhibited autoagglutination and positive reactions to Coombs antiglobulin tests

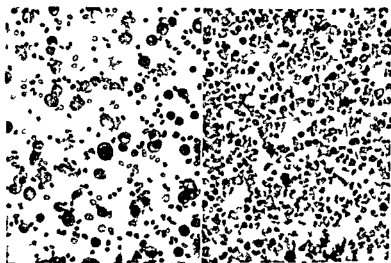
After addition of 100 units/ml penicillin and streptomycin suspensions prepared from whole clotted blood and spleen fragments by grinding with alundum in nutrient broth were injected into embryonated eggs by the allantoic amniotic and yolk sac routes After incubation evidence for growth of viruses was sought by chick embryo examination and hemagglutination tests on allantoic and amniotic fluids with chicken erythrocytes Three serial blind passages were carried out in each instance and fluids or yolk sac tissues from final passage were inoculated on the chorioallantoic membranes of embryonated eggs

These virus isolation technics which should be adequate for such agents as Newcastle disease influenza mumps and psittacosis viruses and probably suitable for herpes and certain pox viruses gave no evidence for the presence of viruses in the blood of these patients thus failing to substantiate previous reports

Splenectomized Case of Paroxysmal Nocturnal Hemoglobinuria (Marchiafava Nazari Micheli Syndrome) Bo Anderson[4] (Karolinska Hosp) states that this disease is characterized by continuous intravascular hemolysis and hemoglobinemia with attacks of hemoglobinuria typically induced during sleep The etiology is unknown There is some abnormality of red blood cells which makes them susceptible to injury by a factor in the patient s blood serum Diagnosis can be made by the Ham Horack test which is used to investigate the hemol

(3) J L b & Cl M d 40 9 4 D mt 195
(4) A t m d ɜ 143 197 06 195

ously the rise being paralleled by the finding of many late erythroblasts in the marrow (Fig 47) A distinct granulocytosis preceded the increase in reticulocytes After the reticulocyte response there was rapid improvement with regard to the anemia The icterus index varied between 4 and 6 during the entire period of crisis There was no evidence of hemoglobinemia or hemoglobinuria during the illness Results of repeated Coombs tests were negative Two of the brothers



Fg 46 (l ft) —Ma w m ght d s fte t f ll e sh w g e yth d hypopla enl g d f m × 50 R t c locyt 0 7%
Fg 47 (ght) —M w m 11 d y aft t f ll s h w g e s mpt f yth p l g d f m ×250 R t l yt 17%
(Co te y f B ttl J D Jr Am J M S 224 8 9 J ly 1952)

were later treated by splenectomy with uneventful recoveries

Occurrence of the crisis in several members of one family with incubation periods of a few days or weeks between cases is presumptive evidence that infection may precipitate the attack Owren has shown that the average life span of the spherocytes in this disease is about 15 days With temporary cessation of red cell formation the red blood count would be reduced approximately one half in about seven or eight days The profound microspherocytosis and low mean red cell diameter observed during the height of the crisis may be explained by the absence of reticulocytes at this time

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(3) J L I & Cl M d 40 9 4 D mb 195
(4) A ta m d sca d 143 397 0f 1952

ysis of the patient s erythrocytes in acidified blood serum from normal persons There is no known therapy and the untreated disease sooner or later has a lethal course

Man 25 had had black nocturnal urine with increasing frequency and severity since age 18 He had severe fatigue dyspnea and palpitation on exertion Paroxysmal nocturnal hemoglobinuria occurred three to four times a month Physical examination revealed nothing noteworthy except moderate splenomegaly Blood hemoglobin level was 60% erythrocyte count as low as 2 700 000 bleeding time 1 minute 30 seconds and coagulation time 9 minutes 25 seconds There was no increased fragility of red corpuscles hemolysis began at 0 52% NaCl and was complete at 0 34% The acid serum test result (Ham and Horack) was positive

Splenectomy was decided on While awaiting surgery in the hospital the patient had severe massive hemoglobinuria of the nocturnal urine Daytime urine showed no hemoglobin Upper respiratory infections and anxiety increased the hemoglobinuria After the enlarged spleen which was normal histologically was removed his general condition greatly improved He was able to resume normal activity Although the nocturnal hemoglobinuria had not completely disappeared its frequency and severity were greatly reduced Hemoglobinemia was much less than preoperatively Hemoglobin level had risen to 75% and the red blood cell count to 3 600 000 Bleeding time was 1 minute 42 seconds and coagulation time was 5 minutes 19 seconds hemolysis began at 0 46% and was complete at 0 25

Removal of the spleen was thought to decrease hemolysis since storage of blood in the spleen during sleep was believed to facilitate acidification of the blood with consequent increased hemolysis The authors recognize that splenectomy may not be helpful in many instances of this disorder but regard it as justifiable in severely anemic patients especially when the spleen is large

Splenic Hemolytic Anemia Treatment by Splenectomy is discussed by Knut Aas[5] (Rikshosp Oslo) who studied 23 patients with various blood diseases including leukemias Hodgkin s disease myelofibrosis aplastic anemia Felty s syndrome reticulosis and latent hemolytic anemia of unknown origin All but two had splenomegaly Hemolytic anemia was demonstrated in 21 The usual clinical and laboratory signs of increased blood destruction were not pronounced Increased red blood cell destruction could be demonstrated with certainty only by erythrocyte life span studies employing the differential agglutination method of Ashby Red cell abnormalities agglutinins or hemolysins could not be demonstrated In

(5) A ta ch r sc d nav 104 111 123 1952

creased red cell production as evidenced by reticulocytosis was absent The hemolytic mechanism therefore was clinically latent demonstrable only by differential agglutination technics

The 50% survival time of transfused cells was distinctly shortened The curve of decline was mostly exponential a possible indication of random destruction Anemia was hypo

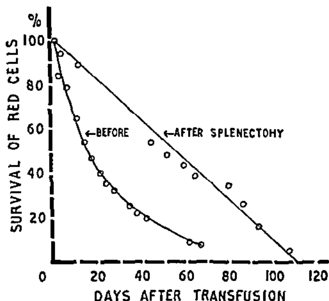


Fig 48 —S rv al f t f d d c ll m p tent w th F lty ynd m nd m B f plen ctomy 50% rv l t m w 17 d y aft per t t w orm l (Cou t y of A K Act h ca d na 104 111 123 1952)

normo or hyperchromic and normocytic No correlation was found between splenic size and severity of anemia

Splenectomy was performed on six patients One died of heart failure postoperatively The hemolytic mechanism ceased in four (Fig 48) and was reduced in one Early splenectomy is indicated in patients with splenomegaly and evidence of increased red cell destruction as demonstrated by survival time of transfused red cells Operation may be of real value in cases of aplastic anemia with such hemolysis It is also indi cated in patients with extramedullary hemopoiesis if a hemo lytic process of the type described is a predominant feature of

the anemia When the underlying pathologic process is rapidly advancing as in acute leukemia operation is not indicated

Presence of a diseased and enlarged spleen seems to indicate that the anemia is caused primarily by increased splenogenic destruction of red cells This is confirmed by the excellent response to splenectomy Disturbed maturation with decreased output of red cells from the bone marrow secondary to hyper splenism or dislodgment of erythropoietic tissue must be considered a contributory cause of anemia

[This article emphasizes that increased red cell destruction may be present and detectable only by survival studies of red cells We do not share the author s belief that fecal urobilinogen studies are of no value in detecting such a process However it has been shown by others that the absence of reticulocytosis and jaundice do not exclude increased red cell destruction —Ed]

Treatment of Acquired Hemolytic Anemia with Compound F Acetate M C Rosenthal T H Spaet H Goldenberg and W Dameshek[6] (Tufts College) report results of compound F acetate therapy in four patients with acquired hemolytic anemia circulating antibodies of the hemagglutinin variety and a positive direct Coombs test Three were considered to have symptomatic hemolytic anemia since in addition to the hemolytic anemia each had the blood and bone marrow findings of chronic lymphocytic leukemia The fourth patient had no demonstrable associated disease

Two patients treated intramuscularly with 150 mg daily showed a partial response but not the usual striking remission or toxic effects seen with intensive ACTH or cortisone therapy Although the need for transfusions was definitely diminished by compound F there was no increase in the red cell count despite a transient reticulocytosis up to 22% in one case and up to 18% in the other In contrast both ACTH and cortisone in comparable dosage in the same patients produced a further reticulocytosis in both patients and a rise in red cell count in one The difference in effects suggests either poor absorption poor utilization or inactivation of compound F acetate at the intramuscular site

Compound F acetate was administered orally to two pa tients in dosage of 200 mg daily One patient had an almost complete remission indistinguishable from that previously achieved in other patients with ACTH or cortisone Toxic manifestations in the form of marked fluid retention and

(6) Lan et 1 1135 1140 Ju 7 195

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To evaluate this new hormone in the treatment of acquired hemolytic anemia further study is necessary

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PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

The first four articles are concerned with the thesis that pernicious anemia is the result of a failure to assimilate vitamin B due to the characteristic lack of gastric secretion The precise mechanism of the normal action of the gastric (intrinsic) factor is unknown It may directly cau e better intestinal absorption or it may prevent competitive utilization of the vitamin by internal bacteria or parasites —Ed

Studies of Excretion (and Absorption) of Co^{60} Labeled Vitamin B_1 in Pernicious Anemia are reported by Robert W Heinle Arnold D Welch Victor Scharf Gordon C Meacham and William H Prusoff[7] (Western Reserve Univ)

METHOD —The radioactive vitamin B_1 used was crystalline cyanocobalamin Co^{60} and consisted of two lots containing 38 and 60 μc /mg respectively With the amounts of vitamin given no patient received more than 0 03 μc /dose (0 5 μg) and no more than six doses Fecal samples were collected separately on wax paper placed in a white enameled pail in a bedside commode The samples were picked up in the paper and both paper and feces transferred quantitatively to a screw top Waring blendor Water was added to give a total volume of 400 ml and the contents were homogenized Under conditions of constant geometry the container was placed adjacent to the crystal of a scintillation counter and compared with standards prepared in a comparable manner from the radioactive vitamin Counting error was ± 5%

Four patients with pernicious anemia (one in relapse and the other three in remission) given radioactive vitamin B_1 orally excreted radioactivity equivalent to 72 96% of the doses On simultaneous administration of an intrinsic factor preparation made from hog stomach to two patients excretion of radioactivity was reduced to less than 5% in one and to 29% in the other Folic acid did not promote utilization of vitamin B_1

These observations suggest that intrinsic factor functions by increasing utilization of orally administered vitamin B_1 through increased absorption This method is suitable for the

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These observations suggest that intrinsic factor functions by increasing utilization of orally administered vitamin B_{12} through increased absorption This method is suitable for the

(7) T A Am Phy na 65 214 2 1952

presumptive assay of activity of intrinsic factor fractions It is rapid and simple and fully treated patients rather than seriously ill patients in relapse can be used

Electrophoresis of Human Gastric Juice in Relation to Castle's Intrinsic Factor A L Latner C C Ungley E V Cox E McEvoy Bowe and Laureen Raine[8] (Univ of Durham and Royal Victoria Infirm Newcastle upon Tyne) report results obtained by preparative paper electrophoresis of concentrated normal human gastric juice at pH 8 6 or 6 35 The purpose was to isolate and to identify its so called intrinsic factor *which when given by mouth potentiates the erythropoietic* activity of vitamin B_1 in pernicious anemia The paper strips employed were cut into sections and the location of protein staining and of vitamin B_1 binding material was determined Several peaks of concentrated protein were demonstrated all of which when eluted from the paper had ability to prevent the utilization of vitamin B_{12} by bacteria Materials from a peak on the cathode and one on the anode side of the starting point on the paper strip were shown clinically to possess intrinsic factor activity The material obtained from the anode peak which was more active clinically was found to contain either a mucoprotein or a mucopolysaccharide The material obtained from the first cathode peak contained much more mucoprotein and may well represent the fraction prepared by Glass and his associates from human gastric juice

Treatment of Pernicious Anemia with Intramuscular Injections of Tapeworm Extracts XIV Diphyllobothrium Latum and Pernicious Anemia Bertel von Bonsdorff and Ruben Gordin[9] (Helsinki) recently showed that dried fish tapeworm like vitamin B_1 when administered with human gastric juice produces remission in pernicious anemia They now report on the effects of two crude aqueous extracts of *dried D latum* injected intramuscularly in five patients who had typical pernicious anemia with characteristic hematologic findings and megaloblastic bone marrow Each solution contained extract of 1 18 Gm dried worm/1 cc Vitamin B_1 activity determined with Lactobacillus leichmanii was 1 μg/1 Gm dried worm for crude extract No 1 and 0 89 μg/1 Gm dried worm for crude extract No 2

All five patients had rapid reticulocytosis and hematologic

(8) Brit M J 1 467-473 Feb 28 1953
(9) Acta med scandinav 144 263 267 1952

response to the extracts without toxic allergic or other untoward reactions during the treatment Four were carriers of D latum Since the experiment was designed to test an extract intended for parenteral injection it is irrelevant whether the patients had cryptogenetic pernicious anemia or pernicious anemia produced by the fish tapeworm

The study indicates that the living fish tapeworm contains large quantities of vitamin B_1 of which the host presumably is thus deprived

[Taken with their other recent observations a possible interpretation may be that the gastric intrinsic factor normally renders the vitamin B less available to the tapeworm or more available to the patient —Ed]

Refractory Macrocytic Anemia with Defect in Vitamin B_1 Binding and with Response to Normal Plasma Results of in vivo studies and of in vitro bone marrow culture studies have suggested that vitamin B_1 is utilized for hemopoiesis in a bound form It was postulated therefore that deficiency in binding might result in refractory macrocytic anemia

Daniel L Horrigan and Robert W Heinle[1] (Cleveland) report observations on a patient with unexplained anemia for 18 years which did not respond to crude liver extract given intramuscularly every week or to an iron compound given orally The stomach contained free HCl During periods of relapse there were macrocytic anemia reticulocytosis and normoblastic bone marrow hyperplasia Remissions were produced by a single intramuscular dose of 90 μg vitamin B_1 or by intravenous administration of 250 cc human plasma After either the hemoglobin level rose from 9 to 12 Gm/100 cc blood and the hematocrit reading from 31 to 40% Remission was not maintained either with 30 μg vitamin B_1 intramuscularly every one to two weeks or 10 mg folic acid daily by mouth On intramuscular administration of 0 5 μg Co^{60} labeled vitamin B_1 60% was excreted in the urine within 24 hours (Normal excretion is 0 10%) After administration of normal plasma urinary excretion decreased to 24% Erythrocyte uric acid was elevated during relapse and normal with remission There was no evidence of increased blood destruction

These observations suggest that the anemia resulted from vitamin B_1 deficiency caused by failure of proper binding and that normal plasma contains a factor which corrects this defect This factor may be (1) binding substance (2) a sub

(1) J Lab & Cl n M d 40 811 812 N mb 195

stance necessary for the combination of vitamin B_{12} and the binding substance endogenously or (3) amounts of the vitamin in bound form sufficient to promote hemopoiesis

[The next three articles relate to the question of whether or not vitamin B_{12} folic acid and thymine or those substances normally present in the plasma will produce maturity of megaloblasts in pernicious anemia marrows in vitro Divergences between the various observations are prominent —Ed]

↓ If the transportation of vitamin B_{12} across the intestinal barrier is normally in some way facilitated by vitamin B_{12} there remains the question of how it is carried thence to the bone marrow The following article describes a presently unique example of possible failure of such a plasma transport mechanism or plasma vitamin B_{12}-binding substance —Ed

Biologic Activity of Megaloblasts of Pernicious Anemia and Effect of Vitamin B_{12} Applied Directly in Vitro C Sacchetti and F da Silva Pirreira (Siena) conclude that proliferation and maturation of megaloblasts in pernicious anemia are not constant but vary according to the patient s condition Culture studies were made of bone marrow from three patients one who had only the ordinary symptoms of pernicious anemia and whose diet was normal one with malnutrition caused by habitual protein deficiency who was unmistakably benefited by iron therapy in the postpernicious phase of his illness and one with enteritis whose blood picture did not improve until chloramphenicol had overcome the infection *It was found* (1) that there are atypical forms of pernicious anemia in which the proliferative activity of the megaloblasts is reduced (2) that vitamin B_{12} added in vitro stimulates proliferation and accelerates maturation and (3) that it also promotes normoblastic transformation of megaloblasts kept alive in a culture medium enriched with embryonal extracts

Megaloblasts of pernicious anemia are differentiated from those of pseudopernicious and macrocytic anemias by morphologic irregularities e g frequent anomalies of mitosis including uneven distribution of chromosomes pluripolarity and polyploidy The rapid replacement of megaloblasts with normoblasts following administration of vitamin B_1 suggests that most if not all of the megaloblasts have been transformed into normoblasts because an increase in the pre existing normoblasts and the production of new proerythroblasts could not take place quickly enough to make such a change in the bone marrow picture *The probability that there is a direct*

(2) H em t l g a 36 1109 1120 195

transformation of the megaloblasts is also supported by the finding of forms intermediate between the megaloblast and the normoblast followed by the appearance and diffusion of normoblastic cell groups just when the proliferative potentialities have been reduced to the minimum (at about 48 hours) The persistence of a small percentage of polychromatophilic and orthochromatic megaloblasts in the late phase of the culture and the mitotic activity of the basophilic megaloblasts in the presence of B_1 suggest that the normoblasts evolve chiefly from the youngest elements the metabolism of which is most easily affected by the vitamin The response occurs only when the culture medium is adequate (containing supplements of normal plasma or embryonal extracts or both) indicating that the vitamin acts as a catalyzer or forms part of a catalyzing system

Observations on Effects of Vitamin B_1, Liver Extracts, Folic Acid and Thymine on Maturation of Megaloblasts in Culture R B Thompson[3] (Royal Victoria Infirm Newcastle upon Tyne) cultured marrow cells aspirated from patients with pernicious anemia in relapse The culture medium consisted of plasma or serum from normal persons or from patients with pernicious anemia diluted with Gey s solution Satisfactory maturation of megaloblasts occurred when 10 50 µg folic acid was added to each milliliter of medium No maturing effect was detected with the addition of 10 100 mµg vitamin B_1 /ml Crude and refined liver extract in concentrations equivalent to 50 mµg vitamin B_1/ml did not cause any maturation nor did concentration of 10 50 and 100 mg thymine/ml

Experiments with these substances in the artificial conditions of marrow culture may well not have any direct bearing on their action in the body However they point to a difference in the mode of action of folic acid and vitamin B_1 Before being utilized in the marrow vitamin B_1 may be altered in some way may require to be bound in the plasma or may act indirectly Further speculation does not appear justified until more information is obtained The various substances probably act at different stages of a chain reaction culminating in the formation of nucleic acids All the pernicious anemia pa

(3) Blood 7 5 525 M y 195

tients whose marrow and plasma were used in these experiments later gave a satisfactory hemopoietic response to vitamin B_{12}

[However according to Horrigan and his associates vitamin B_{12} is active *locally* when instilled directly into the bone marrow cavity in vivo —Ed]

Observations on Behavior of Erythroblasts Cultured in Normal and "Pernicious Anemia" Serums were made by E L Feinmann J Sharp and John F Wilkinson[4] (Manchester Univ)

Several investigators have shown that when megaloblastic bone marrow from a patient with pernicious anemia is cultured the megaloblasts disappear more rapidly from mediums containing normal serum than from mediums containing serum from untreated pernicious anemia Lajtha suggested that the blood in pernicious anemia contains a factor which inhibits the maturation of megaloblasts into either erythrocytes or normoblasts The authors decided to reinvestigate this problem by use of absolute nucleated cell counts and statistical analysis of their results

Technic —Using sterile technic throughout 2 cc sternal marrow was aspirated A few drops were used for diagnostic smears The rest was mixed with 18 ml warm Gey s solution and agitated for 10 minutes The suspension was centrifuged at 2 000 rpm for 15 minutes the supernatant liquid was discarded and the volume made up to 10 ml with Gey s solution The new suspension was mixed and a nucleated cell count made depending on this count the final volume was adjusted to give a nucleated cell count of 15 000 20 000/cu mm Culture tubes were then set up containing 1 ml marrow suspension and varying concentrations of normal and pernicious anemia serums Samples were removed immediately from the culture tube and nucleated cell counts differential smears and pH estimates made The remainder of the culture mixture was incubated at 37 C for 48 hours Specimens were then taken for incubation on blood agar as a test of sterility and pH estimates cell counts and smears were made as before All equipment used in the culturing procedure was silicone treated

Megaloblastic bone marrow from pernicious anemia patients was cultured in mediums containing either pernicious anemia or normal serums When incubated for 48 hours in mediums containing normal serum the decrease in numbers of proerythroblasts and megaloblasts was significantly greater than when the mediums contained pernicious anemia serum

(4) Brit M J 2 14 18 July 5 1952

No evidence has been found that the difference is due to an inhibitory factor in pernicious anemia serum

[One difference between normal and pernicious anemia serum is the low values of vitamin B in the latter —Ed]

Metabolic Studies in Pernicious Anemia I Nitrogen and Phosphorus Metabolism during Vitamin B_1 Induced Remission. G Watson James III and Lynn D Abbott Jr[5] (Med College of Virginia) studied response to vitamin B_1 therapy in four patients with previously untreated pernicious anemia after prescribing a liquid diet low in iron They were given 15 μg crystalline vitamin B_1 initially then 5 μg daily until peak reticulocyte response was attained and 5 μg every other day thereafter A positive nitrogen balance (as much as 6 0 Gm daily) was found in all patients during vitamin B_{12} induced remission Nitrogen accumulated as blood proteins exceeded the dietary intake of nitrogen indicating conversion of tissue nitrogen to blood proteins New hemoglobin formation averaged as much as 17 37 Gm a day and this new hemoglobin nitrogen alone equaled or exceeded the entire dietary nitrogen retained Intestinal absorption of dietary nitrogen was also increased

The phosphorus balance was initially positive then negative co incident with reticulocytosis then positive again Within 48 hours of initial dose of vitamin B_1 urinary phosphorus content diminished As reticulocytes appeared the urine phosphorus level increased but diminished as the reticulocyte response subsided The immediate positive phosphorus balance after vitamin B_1 administration is causally related to the change from a megaloblastic to an erythronormoblastic proliferation in the bone marrow An intense protein generation in the cytoplasm is always correlated with an increase in the cytoplasmic concentration of ribose nucleic acid The phosphorus uptake is related to the formation of increasing quantities of cellular nucleotides and polynucleotides with subsequent formation of the specific protein (globin) of hemoglobin As the synthesis of hemoglobin proceeds nuclear material diminishes and phosphorus is released as a by product of the hemoglobinization Hemoglobin as a protein does not contain phosphorus

Uric acid excretion increases with reticulocytosis and is considered a reflection of accelerated nucleoprotein metabo

(5) M t b l m 1 259 70 M y 195

lism Plasma potassium content decreases during treatment indicating that rapid and increased erythrocyte formation imposes an additional need for this intracellular ion

↓ The next four articles deal with the treatment of pernicious anemia. —Ed

Antianemic Properties of Reaction Products of Vitamin B_{12} and the Intrinsic Factor Tom D Spies Robert E Stone (Birmingham Ala) Ramon M Suarez (Santurce P R) Guillermo Garcia Lopez Ruben Lopez Toca and Alfredo Reboredo[6] (Havana) report on the effects of such *preparations* given orally to patients with pernicious anemia nutritional macrocytic anemia and sprue During control periods of 10 30 days each patient received *daily 10 or 15 μg* vitamin B_{12} without response They were then given daily bifacton tablets containing a similar amount of vitamin B_{12} and an intrinsic factor concentrate Eight patients with pernicious anemia showed striking reticulocyte responses and gains in red cells together with corresponding clinical improvement One patient with nutritional macrocytic anemia and two with sprue and macrocytic anemia did not respond as fully Three other patients with *pernicious anemia known to absorb vitamin* B_{12} *poorly by* mouth even when given with gastric juice failed to respond to bifacton but did so at once following a single injection of 10 μg vitamin B_{12}

In further studies on 11 patients with pernicious anemia a dose of an intrinsic factor concentrate was found to give definite but submaximal effects when given daily with 10 μg vitamin B_{12} This procedure was without benefit in 11 patients with sprue treated in Puerto Rico and Cuba Two additional patients with pernicious anemia responded to the daily oral administration of a preparation of bifacton that had been suspended in water and boiled for 30 minutes

The authors conclude that practical oral therapy with vitamin B_{12} is now at hand for use in selected cases of pernicious anemia On the average patients with pernicious anemia respond better than do patients with tropical sprue to the presently available pharmaceutical preparations of vitamin B_{12} and intrinsic factor concentrate

[Similar results have been obtained by others in pernicious anemia Our past experience with mixtures of gastric juice and beef muscle as well as observations by Spray with gastric juice and vitamin B_{12} makes us skep

(6) J A M A 151 1 641 66 Ap 1 11 1953

tical of the thermostability of the present so called reaction product From the original article it is not clear whether the two patients given boiled bifacton containing 30 µg vitamin B daily had been given a preliminary trial with the same amount of vitamin B_{12} daily alone Occasionally pa tients respond to such amounts of vitamin B_{12} without intrinsi factor Efficient preparations for oral use have been available for many years in the form of desiccated stomach or desiccated stomach liver extract prep arations The present combinations of vitamin B with intrin ic factor concentrate however represent a decid d reduction in the bulk of the product to be swallowed by the patient We remain unconvinced that orally administered vitamin B (potentially self medication) in perniciou anemia is preferable to monthly injection of the vitamin (usually medically su pervised) —Ed]

Studies on Mutual Effect of Suboptimal Oral Doses of Vitamin B_1 and Folic Acid in Pernicious Anemia were made by Edward H Reisner Jr and Leo Weiner[7] (New York Univ Post Grad Med School) in four patients with per nicious anemia megaloblastic bone marrows and histamine refractory achlorhydria Because of the importance of a com parison of degrees of marrow activity as evidenced by reticulo cyte production reticulocyte values are given in percentage and in the absolute number per cubic millimeter

Man 60 in relapse had a blood count of 1 100 000 red cells with 2 1% (23 000/cu mm) reticulocytes After transfusion he was given a daily oral dose of 0 67 mg folic acid At the end of one week reticulocytes were 2 0% (26 000/cu mm) and red cells 1 250 000 He was then given in addition 10 µg vitamin B_{12} by mouth 12 hours after each folic acid administration On the eighth days of combined treatment reticulocyte peak was 12 5% (225 000/cu mm) and red count 1 800 000 A week later reticulocytes had fallen to 2 8% (72 000/cu mm) and red count was 2 600 000 For the next 11 days vitamin B_1 and folic acid were given together No secondary reticu locyte peak was observed and red cell count continued to rise at the same rate to 3 100 000 The patient was transferred to conventional therapy

These studies confirm the findings of Meyer that an en hanced respon e above that due to either substance alone may occur in pernicious anemia treated orally with mixtures of folic acid and vitamin B_1 Since each substance in the dose may have some effect on blood production the simplest explanation appears to be that when they are given together an additive or synergistic effect is produced parenterally i e outside the in testine The authors attribute any synergy between small doses of vitamin B_1 and folic acid in their patients to the fact that traces of B_1 are absorbed—at least in some patients—even in the absence of added intrinsic factor and that these enhance

(7) N w E gl d J M d 247 15 17 J ly 3 195

the effectiveness of the suboptimal but freely absorbable doses of folic acid This phenomenon is inconstant and depends on the ability of the patient to respond to folic acid and on the absorption of some of the orally given B_1 Since the potentiation was observed when the two substances were administered alternately at 12 hour intervals it could not have been due to an intrinsic factor like activity of folic acid with increased absorption of vitamin B_{12} from the gut as with the intrinsic factor of gastric juice origin

Treatment of Pernicious Anemia with Massive Parenteral Doses of Vitamin B_1 was tried by Edward H Reisner Jr and Leo Weiner[8] (New York Univ Post Grad Med School) to discover whether the vitamin might prolong hematologic remissions or cause further improvement in stabilized cases of combined system disease An intramuscular injection of 1 000 μg crystalline vitamin B_1 was given to each of 14 patients with proved pernicious anemia in relapse Complete hematologic remission resulted in all but one patient No further treatment was given until hematologic relapse occurred Four patients were lost from follow up while still in remission at four six eight and nine months after treatment In the other nine remissions lasted from three to seven months In two patients red blood counts exceeded 6 000 000 In one in whom the count has remained high a true polycythemia may have developed

Weekly doses of 1 000 μg were given to six patients with combined system disease which was considered to have been stabilized under regular treatment for two or more years Satisfactory hematologic remissions had been maintained In one patient treated for 13 weeks there was gradual improvement in strength balance position sense and gait but no change in vibratory sense or deep tendon reflexes Improvement continued after return to conventional therapy The authors believe that at least part of it was due to a new effort by the patient to keep ambulatory after being in bed for a year In a second patient treated with massive doses for nine weeks balance and gait improved in the first two weeks but not thereafter The other four patients did not improve after treatment for 10 6 10 and 7 weeks

Urinary assays before and after injection of 100 1 000 μg

(8) Blood 8 81 85 J y 1953

vitamin B_1 showed that 51 98% of the dose was excreted in 48 hours Failure of massive doses to prolong remissions in pernicious anemia or cause improvement in chronic combined system disease is therefore not surprising since the dose re tained was comparable to the regular conventional doses Doses exceeding 50 μg are probably wasted

Reisner and Weiner stress that massive single doses of vita min B_1 cannot safely be substituted for more frequent regular injection of smaller doses in treatment of pernicious anemia and that no improvement in chronic combined system disease is to be expected from weekly injections of massive doses

Maintenance Therapy of Pernicious Anemia with Vitamin B_1 For periods up to 16 months Gordon C Meacham and Robert W Heinle[9] (Western Reserve Univ) gave either crys talline vitamin B_1 or a concentrate containing vitamin B_1 and $B_{1\,b}$ to 43 patients with pernicious anemia An average daily dose of 3 μg of vitamin B_1 concentrate was given to 21 patients and 1 μg of crystalline vitamin B_1 to 9 others 11 patients who had previously been treated with crude liver ex tract or folic acid were given 3 μg daily of vitamin B_1 con centrate and 2 who had been in relapse were given 1 μg daily of crystalline vitamin B_1 After 10 or more months of therapy with the larger dose of vitamin B_1 concentrate or the smaller dose of crystalline vitamin B_1 all but 3 of the 43 patients had attained and maintained satisfactory erythrocyte levels al though macrocytosis (mean corpuscular volume greater than 100 cu μ) was not uncommon Folic acid was given to some patients with macrocytosis but the mean corpuscular volume did not fall below 100 cu μ after five to seven months of ther apy

The study indicates that adequate doses of vitamin B_1 whether crystalline cyanocobalamin (B_1) or concentrates con taining both cyano and hydroxocobalamin (B_{12b}) will control pernicious anemia as effectively as purified liver extracts and that the addition of folic acid accomplishes no more than vita min B_1 or liver extract therapy alone Elevated mean corpus cular volumes in many patients were unexpected There is probably a true difference between the erythrocytes of treated patients and those of persons without pernicious anemia Com parison of treated patients with a normal series from the lit

(9) J L b & Cl M d 41 65 77 J y 1953

erature indicates that the relationship of the erythrocyte level to hematocrit value in the two series differs even when treated patients have high normal blood values This would suggest that vitamin B_{12} purified liver extract or folic acid given singly or in combination does not completely correct the *erythrocyte abnormality in pernicious anemia* and that some additional substance or substances may be required From the practical standpoint however treatment with sufficient vitamin B_{12} B_1 concentrates or purified liver extract maintains normal erythrocyte levels and prevents development or progression of neurologic and lingual lesions

Vitamin B_1 concentrate given every three to four weeks in an average dose of 3 μg daily or crystalline vitamin B_1 given every three to four weeks in an average dose of 1 μg daily is adequate therapy for pernicious anemia

↓ The remaining articles in this chapter are concerned with patients with megaloblastic marrows although usually with a lesser degree of macrocy*tosis than is seen in pernicious anemia Response to folic acid* but not to vitamin B is characteristic —Ed

Infection as Cause of Folic Acid Deficiency and Megaloblastic Anemia Experimental Induction of Megaloblastic Anemia by Turpentine Abscess Infection and ascorbic acid deficiency are common and possibly etiologic features in megaloblastic anemia in infants Megaloblastic anemia usually implies a deficiency of vitamin B_1 or folic acid Since the requirement for folic acid is increased when there is ascorbic acid deficiency and ascorbic acid tends to be depleted during infections some instances of megaloblastic anemia associated with infections may be due to this mechanism However in a survey of the histories of infants with megaloblastic anemia Charles D May Charles T Stewart Agnes Hamilton and R J Salmon[1] (Univ of Minnesota) observed that in most infants anemia developed even when ascorbic acid intake was adequate After a chance discovery that typical megaloblastosis followed the production of sterile abscesses in monkeys by turpentine injection they repeated the experiments to determine the tissue (liver) concentrations of ascorbic acid vitamin B_1 and folic acid and to study the effect of therapy on the marrow The findings were compared with those in healthy controls scorbutic animals and animals with spontaneous infections The ascorbic acid level of the monkeys given tur

(1) A M A Am J Dis Child 84 718 728 December 195

pentine injections was maintained at that of control animals

The liver content of folic acid was considerably below normal in the monkeys with turpentine abscesses In animals with spontaneous infections in which megaloblastic marrows developed folic acid levels were lower than in similarly infected animals with normoblastic marrows In severely scorbutic monkeys folic acid levels remained normal when supplementary folic acid was given Vitamin B_{12} concentrations were less affected in all groups

Neither vitamin B_1 nor ascorbic acid prevented or eliminated marrow megaloblastosis resulting from turpentine injections or developing during spontaneous infections Folic acid was promptly effective in both conditions Megaloblastosis complicating scurvy could be eliminated by either ascorbic or folic acid but vitamin B_1 alone had no effect In the monkeys with turpentine abscesses megaloblastic marrow became normoblastic when the abscesses were allowed to heal

Infants probably do not synthesize folic acid or vitamin B_1 but depend on food and production of these vitamins by intestinal bacterial flora to meet their requirements Normal infants on the usual feeding regimens including adequate ascorbic acid do not require supplementary vitamin B_{12} or folic acid In sick and abnormal infants ingestion intestinal synthesis absorption or utilization may be disturbed or requirements may be increased Requirements could be increased by infection loss of sparing effects rapid growth prematurity or vitamin inhibitors or antagonists Therefore sick infants require special consideration and in cases of severe or prolonged infections it would probably be wise to include additional amounts of vitamin B_1 and folic acid in the treatment

The definitive sign of folic acid or vitamin B_{12} deficiency is a megaloblastic type of hemopoiesis in the bone marrow Apparently both vitamins are required for normal hemopoiesis To determine which is the predominant deficiency in a patient with megaloblastic anemia vitamin B_1 must be tested first because all clinical types of megaloblastic anemia respond to large doses of folic acid regardless of the pathogenesis

Megaloblastic Anemia in Young Adults Etiologic Importance of Occult Idiopathic Steatorrhea is discussed by Hugh Conway (Glasgow) who stresses the potential difficulty

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in differentiating the megaloblastic anemia of idiopathic steatorrhea from addisonian pernicious anemia

Addisonian pernicious anemia is rare under age 30 therefore it was decided to re examine all patients with a diagnosis of addisonian pernicious anemia before age 30 in one medical unit over 13 years Eight were found One had died of refractory macrocytic anemia After study four of the remaining seven were *reclassified as having megaloblastic anemia secondary* to idiopathic steatorrhea

Intestinal symptoms may be of no value in differential diagnosis for steatorrhea may be occult without obvious intestinal dysfunction In patients with no free HCl recognition depends finally on fat balance studies The four patients who were reclassified excreted abnormally high quantities of fecal fat when fed a 70 Gm fat diet over a test period Previously their stools had appeared normal In three of the four persistent histamine fast achlorhydria had led to the original erroneous diagnosis of pernicious anemia Fortunately 60-80% *of patients with idiopathic steatorrhea have free HCl in the* gastric juice after histamine injection

In patients with occult steatorrhea blood calcium and phosphorus contents tended to be normal and deficiencies of fat soluble vitamins were not apparent However *oral glucose* tolerance tests gave a flat curve

Brownish pigmentation of the skin occurs in both diseases but is more marked and more common in idiopathic steatorrhea Digital clubbing a well known feature of idiopathic steatorrhea does not occur with tropical sprue or pernicious anemia X ray examination of the small bowel will in many cases show abnormal patterns characteristic of the sprue syndrome

Erythropoietic abnormality in the patients with addisonian pernicious anemia was fully corrected by parenteral liver *therapy* The patients with idiopathic steatorrhea were refractory to liver except for one who responded completely except *for persistence of macrocytosis* The substitution of folic acid orally in the three refractory patients was decisive resulting *in great hematologic improvement* In addition one patient *required* proteolyzed liver given orally As the red cell count rose hypochromia developed but responded to iron given intravenously

One patient with occult steatorrhea combined histamine fast achlorhydria megaloblastic anemia and an adequate response to parenteral liver therapy making differentiation from addisonian pernicious anemia impossible on clinical grounds The combination of histamine fast achlorhydria and an adequate response to parenteral liver therapy is rarely encountered in steatorrhea This is fortunate for it is impractical to do fat balance studies in all cases of apparently typical pernicious anemia to find isolated cases of steatorrhea

Before the correct diagnosis liver given parenterally was the sole therapy Effectiveness varied from patient to patient and from time to time Nevertheless a fair state of health was maintained Eventually the three patients who remained anemic failed completely to respond to liver The intermediate marrow picture suggested that liver was still minimally effective The megaloblastic marrow of the third reflected complete loss of influence of the liver Folic acid then brought about improvement However other unknown factors are involved for folic acid does not always cure the anemia

Megaloblastic Anemia of Pregnancy is generally considered to be rare In a 1951 study Lund estimated that 1 case of megaloblastic anemia occurs to every 100 cases of iron deficiency anemia In most published cases anemia was severe and was first diagnosed in the puerperium Because of the effectiveness of folic acid therapy early diagnosis is of great practical importance and M C G Israels and F A L Da Cunha[3] (Manchester) believe that many more cases could be discovered during pregnancy if an effort were made to find them They report six cases four of which were diagnosed during pregnancy

Multipara 26 two weeks from term complained of sore tongue gradual weight loss and exertional dyspnea She was not very pale but her tongue was red smooth and swollen Blood studies showed hemoglobin content 11 6 Gm /100 ml red cells 3 100 000/cu mm color index 1 22 and white cell 5,200/cu mm Sternal marrow puncture revealed megaloblastic hyperplasia with many hemocytoblasts and proerythroblasts Gastric acidity was normal Folic acid therapy was begun with 30 mg intramuscularly then 20 mg daily by mouth In a week the tongue was no longer sore or red though still smooth and glazed blood values showed no change Seven weeks after a normal delivery hemoglobin content was 14 2 Gm /100 ml red cell count 4 540 000 color index 1 06 and white cells 5 450 The

(3) L et 2 214 215 A g 2 195

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media uterine infection bronchopneumonia antepartum hem orrhage and pre eclampsia

There are no pathognomonic symptoms by which the dis ease can be recognized There may be the usual symptoms characteristic of severe anemia Five patients had vomiting 2 had diarrhea 4 had edema 7 had sore tongue 1 had an enlarged spleen 2 had enlarged livers 10 had free hydro chloric acid in the stomach and 6 had histamine fast achlor hydria The diet during pregnancy was found to be unsatis factory in at least eight cases

The hematologic findings were the most important The mean hemoglobin was 6 5 Gm /100 ml the mean red cell count 2 210 000 Five patients had a color index above normal eight had a normal index and five a low index Mean corpus cular volume was normal in five above normal in five and below normal in five By all these methods macrocytosis was detected in only seven cases Six patients had a low mean corpuscular hemoglobin concentration indicating hypochromia Examination of the stained blood film often fails to reveal the diagnosis Only six patients had well marked macrocytosis The detection of an occasional macrocyte an immature white cell or a nucleated red cell may give a clue to diagnosis The diagnosis is best made by examination of the bone marrow which was megaloblastic in all these patients

The bone marrow should be examined in all pregnant women with apparently refractory iron deficiency anemia and a red cell count under 3 500 000 Megaloblastic anemia of pregnancy and the puerperium must be differentiated from addisonian pernicious anemia and idiopathic steatorrhea Ad disonian pernicious anemia was definitely ruled out in all but three patients and it is probable that these patients did not have pernicious anemia

Treatment must be directed to the reversal of the bone marrow from the megaloblastic to the normoblastic state Results of treatment with refined liver extract were extremely poor Response to vitamin B_{12} was poor Proteolyzed liver was given to four patients with satisfactory results in three Folic acid was administered to eight patients with good response in all Leuconostoc citrovorum factor was given to one patient who had a satisfactory response All patients

patient's diet revealed no gross deficiencies but for six or eight weeks before treatment she ate almost nothing because of soreness of her tongue One week after the start of folic acid she was able to eat again

Average age of the patients was 29 only one had had anemia before of unknown type in pregnancy Five of the six had sore tongue with or without buccal ulcers five had exertional dyspnea one dysphagia two vomiting late in pregnancy and two short bouts of diarrhea There were no central nervous system abnormalities

Diagnosis in all cases depended on sternal marrow examination The bone marrow picture is sometimes classically megaloblastic but more often there are many procrythroblasts normoblasts and relatively few megaloblasts In early cases transitional erythroblasts and typical large metamyelocytes are seen Gastric analysis is also important Patients with achlorhydria should be followed for at least a year after cessation of therapy to rule out addisonian pernicious anemia Ideally for diagnostic purposes they should be given a course of vitamin B_{12} therapy but usually time is too short

The usual dose of folic acid is 20 mg a day orally If time is short 30 mg a day intramuscularly for three days or 100 mg intravenously may be given Maintenance with daily oral doses of 20 mg should continue into the puerperium until the blood values are normal for one month The patient should be rechecked after cessation of therapy

In some patients on folic acid therapy iron deficiency anemia develops that will require the addition of oral iron therapy If a woman is seen late in pregnancy or has severe blood loss during labor transfusion may be necessary

Since prognosis with therapy is excellent early diagnosis is important Because the peripheral blood picture may be atypical bone marrow aspiration is essential

Megaloblastic Anemia of Pregnancy and Puerperium James K Clark[4] (Univ of Edinburgh) presents 18 of 43 cases seen since 1939 The mean age of the patients was 33 and most had had previous pregnancies The disease usually begins in the third trimester or in the puerperium nine cases were diagnosed before parturition and nine in the puerperium Associated diseases during pregnancy included sepsis otitis

(4) Edinburgh M J 59 74 91 Jan 1952

media uterine infection bronchopneumonia antepartum hem orrhage and pre eclampsia

There are no pathognomonic symptoms by which the dis ease can be recognized There may be the usual symptoms characteristic of severe anemia Five patients had vomiting 2 had diarrhea 4 had edema 7 had sore tongue 1 had an enlarged spleen 2 had enlarged livers 10 had free hydro chloric acid in the stomach and 6 had histamine fast achlor hydria The diet during pregnancy was found to be unsatis factory in at least eight cases

The hematologic findings were the most important The mean hemoglobin was 6 5 Gm /100 ml the mean red cell count 2 210 000 Five patients had a color index above normal eight had a normal index and five a low index Mean corpus cular volume was normal in five above normal in five and below normal in five By all these methods macrocytosis was detected in only seven cases Six patients had a low mean corpuscular hemoglobin concentration indicating hypochromia Examination of the stained blood film often fails to reveal the diagnosis Only six patients had well marked macrocytosis The detection of an occasional macrocyte an immature white cell or a nucleated red cell may give a clue to diagnosis The diagnosis is best made by examination of the bone marrow which was megaloblastic in all these patients

The bone marrow should be examined in all pregnant women with apparently refractory iron deficiency anemia and a red cell count under 3 500 000 Megaloblastic anemia of pregnancy and the puerperium must be differentiated from addisonian pernicious anemia and idiopathic steatorrhea Ad disonian pernicious anemia was definitely ruled out in all but three patients and it is probable that these patients did not have pernicious anemia

Treatment must be directed to the reversal of the bone marrow from the megaloblastic to the normoblastic state Results of treatment with refined liver extract were extremely poor Response to vitamin B_{12} was poor Proteolyzed liver was given to four patients with satisfactory results in three Folic acid was administered to eight patients with good response in all Leuconostoc citrovorum factor was given to one patient who had a satisfactory response All patients

patient s diet revealed no gross deficiencies but for six or eight weeks before treatment she ate almost nothing because of soreness of her tongue One week after the start of folic acid she was able to eat again

Average age of the patients was 29 only one had had anemia before of unknown type in pregnancy Five of the six had sore tongue with or without buccal ulcers five had exertional dyspnea one dysphagia two vomiting late in pregnancy and two short bouts of diarrhea There were no central nervous system abnormalities

Diagnosis in all cases depended on sternal marrow examination The bone marrow picture is sometimes classically megaloblastic but more often there are many proerythroblasts normoblasts and relatively few megaloblasts In early cases transitional erythroblasts and typical large metamyelocytes are seen Gastric analysis is also important Patients with achlorhydria should be followed for at least a year after cessation of therapy to rule out addisonian pernicious anemia Ideally for diagnostic purposes they should be given a course of vitamin B_{1} therapy but usually time is too short

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(4) Ed bu gh M J 59 274 291 J n 1952

observed Administration of folic acid to one patient resulted in disappearance of anemia and of orthochromatic erythro blasts and fragmentation of Howell Jolly bodies It was felt that response demonstrated an influence of folic acid on the spleen [more likely a lessened demand on the bone marrow for erythropoiesis because the anemia was abolished —Ed]

Folic acid deficiency resulting in the megaloblastic anemia of pregnancy or puerperium is associated with splenomegaly Such cases are usually of short duration time may be an important factor in development of atrophy Atrophy of the spleen has been reported in rats fed folic acid deficient diets Folic acid is thought to be necessary to cytopoiesis and has been shown to play a role in the synthesis of desoxyribose nucleic acids a component of chromosomes whose metabolism is rapid in the spleen Therefore atrophy of the spleen is probably due to a disturbance of cellular regeneration second ary to chronic folic acid deficiency

Symptoms Signs and Diagnostic Features of Idiopathic Steatorrhea Idiopathic steatorrhea is characterized by mild chronic ill health recurrent glossitis anemia and variable degrees of intestinal upset There is a significant familial inci dence Diagnostic criteria include abnormal fat absorption as demonstrated by fat balance technics disturbances of the hemopoietic system and a deficiency pattern in x rays of the intestinal tract

W Trevor Cooke A L P Peeney and C F Hawkins[6] *(Birmingham Univ) studied the disease in 49 men and 51* women who were observed 2 10 years Fourteen patients died There were three main groups of symptoms (1) constitutional disturbances such as lassitude weight loss glossitis and symp toms of anemia (44 patients) (2) diarrhea (43) and (3) miscellaneous symptoms of a neurologic nature backache or gastric symptoms (13) The commonest symptom was lassi tude (Fig 49) All but 20 patients had a disturbance of bowel habits A common feature was attacks of loose stools or actual watery diarrhea lasting for a few days three to four times a year The stools were usually paler than normal offensive and often frothy Long car journeys spells of extra work overtime in the factory and overindulgence in fatty or fried food precipitated the diarrhea Abdominal symptoms such as

(6) Q t J M d 22 59 77 J ry 1953

eventually made a complete recovery Stillborn infants were born to three mothers Three patients eventually became preg *nant again and two had megaloblastic anemia again A fol* low up study 3 months to 7½ years after parturition revealed a satisfactory blood picture in all patients with normoblastic bone marrow

Megaloblastic anemia of pregnancy and the puerperium may be similar or even identical to nutritional megaloblastic anemia which affects both pregnant and nonpregnant women and also men There has been a lack of uniformity in the response of nutritional megaloblastic anemia to different forms *of treatment Watson and Castle believe the diversity of results* following treatment suggests that more than one type of nu tritional macrocytic anemia might occur and that deficiency of a substance found in autolyzed yeast which they suggested be called Wills s factor might be the cause of one Another type might be due to extrinsic factor deficiency The work of Day Wilson and Lurman suggests that Wills s factor might be folic acid but this view does not find general acceptance

The etiology of megaloblastic anemia of pregnancy is unknown It may be a deficiency disease due to lack of folic acid in the diet It is possible that more than one type of deficiency occurs and that cases of megaloblastic anemia of pregnancy and the puerperium do not form one homogeneous group

[Some of the confusion concerning response of nutritional megaloblastic anemias to therapy appears to have resulted from the use of excessive doses of vitamin B_{12} If a megaloblastic anemia is based on partial deficiencies of both vitamin B_{12} and folic acid it may be expected to respond to large dosage of either All nutritional macrocytic anemias including pernicious anemia respond at least initially to folic acid We suggest that a limiting deficiency of vitamin B_{12} may be excluded (or confirmed) by the daily intramuscular injection of 1 µg vitamin B A reasonable daily test dose of folic acid by this route of administration would appear to be 250 µg —Ed]

Erythroblastic Anemia A Manifestation of Folic Acid Deficiency H O Nieweg and A Arends[5] (Univ of Groningen) found atrophy of the spleen at autopsy in three patients with nontropical sprue one with chronic glomerulonephritis fed a deficient low protein diet and one with Whipple s disease The presence of orthochromatic normoblasts and Howell Jolly bodies in the peripheral blood was thought to be a manifesta tion of splenic atrophy *Extramedullary hemopoiesis was not*

(5) Blood 8 175 181 F b ua y 1953

had mild pyrexia Edema of the dependent parts occurred in 34 Low blood pressure was common Some patients had decalcification of the bones

Examination of the intestine with a flocculating barium emulsion revealed a deficiency pattern in 75 patients so examined Severe anemia was not common the red blood cells usually being 3 000 000-3 500 000/cu mm the hemoglobin between 11 4 and 13 1 Gm /100 cc Microcytosis was rare even in patients with severe hypochromic anemia Even with iron deficiency the mean cell diameter was increased blood films commonly showing a mixture of large and of normal sized erythrocytes Macrocytosis was present in two thirds A few had a peripheral blood picture indistinguishable from pernicious anemia All patients in whom megaloblasts were seen had erythrocyte counts below 2 900 000

The mean fat absorption during a three dav balance test was 74 8 ± 12 25% The authors lower limit of normal values is 94 6 ± 1 9% Microscopic examination of the feces showed an excess of fatty acid crystals in 85 patients

The serum sodium content was low in many patients as was the serum potassium Total plasma cholesterol values were low in many patients Duodenal intubation was carried out in 34 and the values for amylase lipase and trypsin were all within normal limits

In patients with atypical anemia or chronic diarrhea a fat absorption test must be considered an essential procedure

[But *how* essential i it? As remarked by the authors It is difficult to unde stand why a patient who ab orb 85 to 87 per cent of ingested fat should have symptom whereas one who ab orbs 90 per cent or more is unlikely to have such symptoms In view of the fact that characteristic refractory anemia may be pre ent in two members of a family one of whom may have normal fat absorption it would appear that steatorrhea is not a *sine quo non* Moreover if lassitude is the most rel a ble symptom of the d sease it may be well to consider that the disturbance of intestinal function may be a reflection of a more generalized systemic disturbance —or even of more than one condition —Ed]

HYPOCHROMIC ANEMIAS

Iron Metabolism Clinical Evaluation of Iron Stores Alexander R Stevens Jr Daniel H Coleman and Clement A Finch[7] (Univ of Washington) state that marrow examination

(7) A I t Med 38 199 05 F bru y 1953

flatulence nausea vomiting and epigastric pain were usually mild Appetite was good in most patients All but three had had loss of weight Four patients had some form of tetany

Purpura was present in 10 patients There were mild forms of anxiety in a few patients Glossitis was present in 90 Hypokalemia necessitating treatment was present in 10 In 43 patients the disorder had its onset in childhood The disease

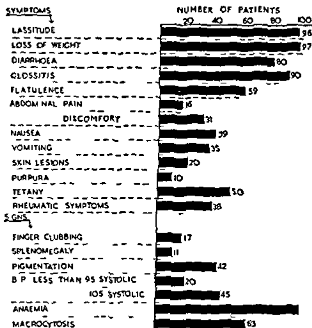


Fig 49 —I d f m n s mpt m d s g n 100 pat t with id p thc ste t rrhea (Cou tesy f Cook W T et l Q t J Med 2 59 77 Ja y 1953)

had no effect on pregnancy or virility A family history of steatorrhea was present in 10 There were few associated dis eases except rheumatism Active or healed tuberculosis was present in five The patients had a characteristic facies giving a triangular appearance from the front there was a prominent zygomatic arch and a narrow jaw Premature graying of the hair was common and the beard grew poorly but baldness was not encountered Pigmentation and skin rashes were present in some cases Clubbing of the fingers occurred in 17 Some

prussian blue reaction This method allows the staining of the iron in the reticuloendothelial cells in situ and obviates the artifacts that are usually seen in stained smears of bone marrow Stained marrow sections were prepared from 141 patients who were either normal or had some anemia When present the iron is usually found both as densely stained granules and as diffuse pale blue discoloration of the cytoplasm of the cells It occurs both in the extravascular reticulum and littoral cells of the vascular sinuses In marrows containing little stainable iron a diffuse blue coloration of a few cells may be all that is seen When large masses of pigment are present it is sometimes difficult to be certain that it is still intracellular and not lying free in the tissues

In all 17 subjects who had no evidence of disease of the blood bone marrow sections showed normal iron staining Marrows from those with anemia showed variation in the amount of stainable iron ranging from total absence of stainable iron through normal staining to gross excess Of 30 anemic patients with marrows devoid of stainable iron actual iron deficiency was clinically evident in the presence of an anemia of low mean corpuscular hemoglobin concentration or there was a clear history of blood loss indicating the probability of occult deficiency In many of these patients the administration of iron was clinically beneficial and when in a few instances sternal puncture was repeated after the hemoglobin returned to normal stainable iron had returned to the marrow In five patients with marrow totally devoid of stainable iron no clearcut clinical evidence was obtained although these patients probably had iron deficiency

Marrows containing approximately normal amounts of stainable iron were found in patients with a great variety of diseases of the hemopoietic system These patients do not require iron therapy Marrows containing a definite excess of stainable iron were found in two types of anemia (1) marrows with a hemolytic element and (2) marrows of aregenerative type whether this was due to primary marrow failure as in aplastic anemia or to depression of marrow function the result of chronic intoxication as in secondary anemia Knowledge of an excess of stainable iron is a useful additional indication of marrow failure in anemias of the aregenerative type it indicates that the iron is reaching the marrow from

for hemosiderin is a reliable index of iron stores and is frequently the decisive test in diagnosis of anemia due to iron deficiency A total of 298 marrow examinations was made in 31 patients with normal blood findings 73 with iron deficiency anemia 46 with anemia associated with infection 20 with cirrhosis 25 with untreated pernicious anemia 30 with malignant disease without blood loss 9 with uremia and 12 with hemolytic anemia About 3 cc of marrow was aspirated and mixed with an equal volume of 4% sodium citrate solution Unstained smears of bone marrow were examined for hemosiderin granules or were then stained with prussian blue Iron content was graded as none slight moderate or heavy

Normal subjects had a slight amount of marrow iron In patients with iron deficiency anemia the marrow iron was either absent or present in minute amounts In most of those with anemia associated with infection there was an increase in iron stores In the other disease states associated with anemia but no known blood loss such as cirrhosis pernicious anemia nonbleeding malignant lesions uremia and hemolytic anemia the amount of marrow iron was usually increased

In the development of iron deficiency anemia the earliest change is the contraction of the iron reserve Clinical evaluation of this iron reserve should allow early detection of iron deficiency The iron content of the reticuloendothelial system can be determined by marrow aspiration No stain is needed to see the golden refractile hemosiderin granules but it is most important that particles of marrow tissue be examined since few reticuloendothelial cells are seen among free marrow cells In infection iron is shifted from the red cell mass to tissue stores as anemia develops since appreciable iron cannot be excreted this shift is reflected in increased amounts of marrow iron

The determination of marrow iron content is the best means of differentiating iron deficiency anemia from anemia due to infection Unless iron is reduced or absent in the marrow a patient will not benefit from iron therapy

Significance of Stainable Iron in Sternal Marrow Sections Its Application in Control of Iron Therapy H E Hutchison[8] (Western Infirm Glasgow) estimated the amount of stainable iron in histologic sections of sternal bone marrow by the

(8) Blood 8 236 248 M ch 1953

able iron administered to patients in group A was 4 900 mg Patients in group B received an average total dose of 1 359 mg

The liquid ferrous gluconate preparation was by far the most popular with the patients Many who were given ferrous sulfate asked for a change to the other medicine

[This kind of comparison is difficult The groups are small the patients in group A were more anemic than those in group B and whether some hemoglobin regeneration would not have taken place without iron therapy is unknown —Ed]

Iron Absorption Tests in Anemia Use of Intravenous Iron Preparations Joan Crawley[1] (University of Edinburgh) carried out iron absorption tests on 6 normal subjects 34 patients with hypochromic anemia who subsequently responded to oral iron therapy and 5 patients with hypochromic anemia who were refractory to oral therapy but subsequently responded to intravenous therapy Oral administration of a test dose of 18 gr ferrous sulfate to the normal subjects produced an average rise in serum iron of 145 μg/100 cc (Fig 50) The value of 100 μg/100 cc was taken as the arbitrary lower limit of normal in persons receiving a dose of about 4 mg iron/kg body weight Average rise in serum iron was 236 μg/100 cc for 19 patients with iron deficiency anemia and 223 μg for 15 with allegedly refractory iron deficiency anemia All later responded to oral iron therapy These levels indicate normal absorption of iron from the gastrointestinal tract Average maximal rise in serum iron was 31 μg/100 cc for five patients with allegedly refractory iron deficiency anemia The poor response indicates that the gastrointestinal tract was not absorbing iron These patients did not respond to oral iron therapy but responded well to intravenous therapy—saccharated oxide of iron (ferrivenin) in divided doses to a total of 1 1 8 Gm

Absorption tests were carried out on seven patients with addisonian pernicious anemia and two with macrocytosis with normoblastic or macronormoblastic marrow Average fasting serum iron for the 10 patients was 138 μg/100 cc with a rise of only 27 μg after oral iron administration That for the seven with pernicious anemia was 174 μg/100 cc with a rise of 18 μg The serum iron level in pernicious anemia invariably falls within the first few days after specific treatment This is supposedly due to rapid utilization of the iron by the newly formed red cells and usually follows the reticulocyte rise

(1) Ed b gh M J 59 478 491 O tob 195

the breakdown of old cells but the marrow is unable to resynthesize it normally into hemoglobin

The staining of bone marrow sections with prussian blue provides a simple means for control of iron therapy in anemias Absence of stainable iron indicates iron deficiency If stainable iron is present the anemia will not be improved by administration of iron either by mouth or intravenously The method is a possible means of distinguishing the hypochromic anemias of chronic intoxication from those due to iron deficiency

Therapeutic Response of Secondary Anemias to Organic and Inorganic Iron Salts Since the discovery that only ferrous iron can be used by the hemopoietic system inorganic ferrous salts have provided the standard form of iron therapy Because gastric intolerance to ferrous salts causes many patients to discontinue treatment David Haler[9] (Westminster Hosp) investigated the therapeutic effects of organic ferrous gluconate in iron deficiency anemias Ferrous gluconate is the normal ferrous salt of d gluconic acid is a dihydrate crystal and contains 11 5% ferrous iron

Forty four patients with anemia following postpartum hemorrhage normal delivery or an illness were selected at random Various inorganic iron preparations plus supplementary vitamins when indicated were given to 21 patients (group A) A liquid organic iron preparation which contained aneurin hydrochloride nicotinamide riboflavin and vitamin C was given to 23 patients (group B) The daily intake of available iron by patients given ferrous sulfate was about 180 mg The ferrous gluconate provided 105 mg /day Therapeutic response was assessed according to (1) total increase in grams of hemoglobin/100 ml (2) average daily hemoglobin increase/100 ml (3) iron utilization coefficient calculated on the basis that 30 mg iron is required to raise the hemoglobin by 1% and (4) average number of treatment days required to raise the hemoglobin level to normal

Average hemoglobin increase was 2 9 Gm /100 ml in group A and 3 4 Gm /100 ml in group B In group A mean daily hemoglobin increase was 1 02% and in group B 1 49% The iron utilization coefficient was 18 1 in group A and 28 3 in group B and the average number of treatment days was 21 7 in group A and 17 8 in group B Average total dose of avail

(9) B M J 1 41 1243 Dec 19

administration of ferrous sulfate indicates satisfactory iron absorption Most patients with hypochromic anemia showing such a rise can be expected to respond to oral iron therapy given under supervision In addition to patients with malab sorption there is a group with no evidence of blood loss splenic anemia carcinoma faulty diet or diarrhea whose serum iron curves are persistently flat Parenteral iron therapy is necessary for these patients

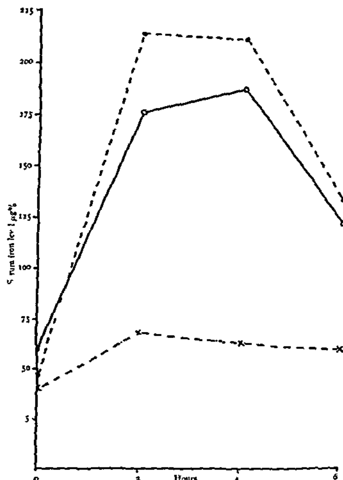
Indications for intravenous iron therapy are (1) persistent gastrointestinal disturbance as a result of oral iron therapy as is commonly found in pregnancy (2) malabsorption of iron due to persistent diarrhea steatorrhea or gastric or small gut resection and rarely idiopathic malabsorption of iron (3) rheumatoid arthritis and (4) depletion of iron stores in the body after massive external loss of iron necessitating rapid restoration

Toxic Reactions Due to Intravenous Iron. I M Librach (Ilford Isolation Hosp) discusses the reactions in two tuber culous patients and reviews theories on the causation of iron intoxication In one patient the manifestations were epilepti form fits lumbar and chest pain burning sensations flushing and sweating The other patient an asthmatic had symptoms predominantly of bronchospasm but also had headache limb pain pallor flushing and faintness

Intravenous iron intoxication seems dependent on two factors the iron transport mechanism and allergy Some investigators feel that toxic reactions occur only when the serum iron binding capacity is exceeded This capacity is dependent on the quantity of unsaturated siderophilin avail able which varies with the state of the iron stores protein metabolism anemia infection and other factors

As iron transport seems dependent on an iron protein com plex this protein component could well account for anaphy lactic phenomena such as bronchospasm Desensitization may be achieved by using graduated doses of iron the desensitiza tion being due to the increase in encompassed protein rather than to the iron directly Delayed reactions have been reported which Librach believes represent a type of serum reaction It has been suggested that long intervals between injections predispose to reactions Foster Kennedy stresses the impor

(2) B t. M J 1 21 24 J 3 1953



F g 50 —I n abeo pt n curv aft te t dos f 18 g f ou ulf te S l d ho m n f 6 n rm l bjects b oken l m n f 34 m pat t wh re spo d d t n gi n rally b ken l e w th d ts m n f 5 m pat ents wh f led t espo d to r n g en lly b t ponded to n gi n ntra ou ly (Court y f Cr wl y J Ed nl u gh M J 59 478-481 Octobe 1952)

Iron excretion studies indicated that there is no apparent excretion into the intestinal tract that the kidneys are capable of limited excretion varying from 29 to 44% of a 200 mg injection and that the urinary excretion is not directly related to the hemoglobin level

A rise of serum iron above 100 μg/100 cc. after oral

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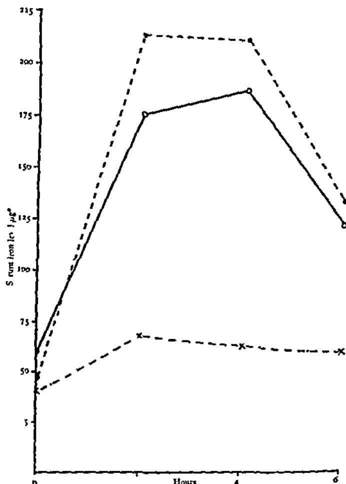
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(2) B r M J 1 124 Jan 3 1953



F g 50 —Iro bso pt on cur es afte test dos of 18 g f o lf t Sol d lin n an f 6 n mal bject b oken l mean of 34 a em p t nt wh e spond d to n gi n ally b k n l n w th d t m n of 5 m c p t t who fa l d t e p nd to t n g n o ally b t ponded t n gi en nt t nous y (Cou te y f C awley J I d b rgh M J 59 478 491 Octobe 195)

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the article by Erslev Fortunately discontinuance of the drug at the onset of clinical or laboratory abnormalities has sometimes been followed by recovery of bone marrow function However the possibility must be considered that as is apparently the case with other cyclic compounds damage to hemopoietic structures may only become apparent weeks or months later —Ed

Chloramphenicol and Aplastic Anemia Jack J Rheingold and Carroll L Spurling[3] (Washington D C) review the literature and report five cases of fatal aplastic anemia believed due to chloramphenicol

CASE 1 —Woman 31 received 15 capsule of chloramphenicol in December 1951 for an upper respiratory infection and 6 capsules in January 1952 for a total dose of 5 5 Gm Urticaria developed when the second course was given and la ted a few days In February 1952 petechiae appeared on the arms and legs Examination revealed severe pancytopenia with a hypocellular marrow She was treated with ACTH vitamin B_1 ascorbic acid vitamin K and repeated blood transfusions but became progressively worse and died At autopsy petechiae and hematomas were seen all over the body

CASE 2 —Man 23 took 24 capsules of chloramphenicol in November 1951 for sinusitis and repeated the course early in December On December 10 he noted petechiae all over the body and during the next two month became extremely weak In February 1952 he had epistaxis Studies showed severe pancytopenia and a hypocellular bone marrow During this hospital stay he again received 24 capsules of chloramphenicol The total dose was about 18 Gm Despite treatment with blood transfusions vitamins penicillin aureomycin and terramycin he died about 145 days after on et of the illness Autopsy revealed many petechiae and many foci of bacteria and fungi

CASE 3 —Girl 18 with recurrent furunculosis stated that for two weeks in August 1951 she took 1 capsule of chloramphenicol every three hours while awake although according to her physician s record a short course had been given in June and another in July There was no record of medication in August Early in October she began to have scattered ecchymo es Late in October she took 2 capsules of the drug without the physician s advice In November petechiae appeared At that time she was found to have severe pancytopenia with a hypocellular bone marrow She died of overwhelming gastrointestinal hemorrhage in February 1952

CASE 4 —Woman 36 with a chronic leg ulcer and a positive reaction to a syphilis test was treated with a total of 61 Gm chloramphenicol in July and August 1951 When discharged she continued to take the drug for three weeks (dosage unknown) In November she noted petechiae and ecchymoses Examination revealed aplastic anemia About four months before onset of the aplastic process she had received sulfisoxazole and variety of other medicaments including aureomycin pharyngets She had evidence of thrombopenia leukopenia and anemia and died of an overwhelming

(3) J A M A 149 1301 1304 A g 2 195

tance of allergy in central nervous system disease Spencer studying ferrous sulfate poisoning in children concluded that iron interfered with cell function particularly in the central nervous system This could well be due to allergy

Iron may displace copper from its protein substrate and reactions may be due to free copper Immediate pain in the limbs and back may be caused by venospasm secondary to temporary concentrations of free iron compound at the moment of injection

Toxic reactions occur independent of the iron compound used Dimercaprol increases the toxic manifestations The severity of the reaction depends on the dosage of iron the most severe reactions following doses of over 100 mg Death may be due to widespread interference with cell function possibly on an anaphylactic basis

— —

OTHER ANEMIAS

During the past year the attention of the medical profession has been drawn to another example of a drug with toxicity for the hemopoietic organs Previous experience with organic arsenicals amidopyrine sulfonamides thiouracil tridione® and mesantoin® for example clearly indicates that certain useful drugs may be hazardous in a few individuals However when a drug is widely used in a sufficiently large number of persons the absolute number of persons adversely affected becomes perceptible Moreover when the attention of the medical profession is attracted by reports of a few cases the literature shortly may become flooded with similar examples Such appears to be the situation with respect to chloramphenicol the first of the naturally occurring antibiotics to be synthesized on the basis of the model compound obtained from an actinomycete

Smadel pointed out in 1949 that this substance a nitrobenzene compound might be toxic for the hemopoietic system However pharmacologic studies showed no evidence of toxicity except for a mild transient anemia in dogs In 1950 Volini reported reversible granulocytopenia and bone marrow hypoplasia in three patients A few scattered reports followed but in 1952 articles began to appear which taken all together make it certain that following even short single courses of the drug but more often with repeated or prolonged use thrombocytopenia agranulocytosis or pancytopenia may develop Clinical circumstances have suggested both sensitivity reactions and acute and chronic suppressions of the bone marrow

Only a few of the many articles on the toxic aspects of chloramphenicol published during 1952 appear in abstract form in this chapter In the originals the reader will find ample documentation In general the use of chloramphenicol must be regarded as potentially hazardous Therefore it should be employed only in serious types of infection which are not adequately controlled by other drugs Frequent blood examinations yielding normal results may give a sense of security that is not justified but they will probably give warning in some instances such as those described in

treated with 155 5 Gm of chloramphenicol in 50 days and the other with 66 5 Gm in 24 days Both had received small amounts of other drugs before and during chloramphenicol therapy When use of the antibiotic was discontinued a striking reticulocyte response occurred along with reappearance of normoblasts in the bone marrow This indicates a direct relation between administration of chloramphenicol and the observed erythropoietic hypoplasia

During treatment there was a gradual decrease in the total leukocytes especially the neutrophils in both cases Bone marrow examination revealed myeloid maturation arrest at the metamyelocyte stage Before this examination the leukocyte counts had not been regarded as unusual It seems significant however that when use of the drug was discontinued the circulating leukocytes increased in both cases Megakaryocytes and platelets were not influenced significantly Final hematologic diagnosis was reversible erythropoietic hypoplasia with myeloid maturation arrest induced by chloramphenicol

Because of a nitrobenzene ring in its structure chloramphenicol had been considered a potential bone marrow toxin So far it has been implicated in 40 cases of maturation arrest or hypoplasia of one or more bone marrow elements Twenty seven cases were fatal In most of these it has been difficult to prove beyond doubt that chloramphenicol was responsible However since in eight discontinuance of the drug resulted in immediate recovery it seems justifiable to assume that bone marrow depression in all these cases was caused by the antibiotic The changes encountered have ranged from mild reversible maturation arrest to severe irreversible aplasia In most instances large doses or prolonged treatment was given

Bone marrow depression due to chloramphenicol is considered rare It is possible that hematologic changes observed in infectious diseases treated with this drug are too often attributed to the infection

All patients receiving chloramphenicol should be closely followed by hematologic study including red blood cell count white cell count and stained smear since drug induced bone marrow depression in its early reversible form may involve erythropoiesis myelopoiesis or thrombocytopoiesis independently Bone marrow examination should be used to check any

staphylococcus bacteremia Although the patient took many medicaments chloramphenicol was the last agent used

CASE 5 —*Woman 26 took 1 Gm chloramphenicol daily for two* months for acne and eczema Menorrhagia began 23 days after use of the drug was stopped because of nausea She was found to have aplastic anemia and an extremely hypoplastic bone marrow Penicillin and cortisone therapy were given but she died later

Aplastic Anemia Associated with Administration of Chloramphenicol Malcolm M Hargraves Stephen D Mills and *Frank J* **Heck**[4] *(Mayo Clinic) report on eight cases of aplastic* anemia referred to them over 11 months in which a history of ingestion of chloramphenicol was established Included also are four other cases obtained through the co operation of physicians The case histories resemble those of other writers Most of the patients had taken the drug for a few hours rather than for days or weeks Purpura appeared about four weeks after the precipitating course of treatment and all fatalities were the result of uncontrolled hemorrhage As in other types of aplastic anemia no specific treatment was of benefit

The authors observed at least three different types of exposure and response patterns The first suggested a sensitivity mechanism Thus in four cases a second course of treatment seemed to precipitate the bone marrow failure *In* two of these nausea and vomiting promptly followed the beginning of the second period of drug administration In two *patients only four capsules of the drug constituted* what appeared to be the precipitating dose A single course of chloramphenicol appeared to result in acute marrow aplasia 18 capsules of 50 mg each in one case and 42 capsules of 50 mg each in the other A more gradual failure of the bone marrow seemed to result in one patient from daily ingestion of 250 mg for six months Another patient took 160 180 capsules intermittently during a period of nine months In some patients other types of chemotherapy including aureomycin and sulfonamides had been given Six of twelve patients died Three have continued to have abnormal blood pictures The outcome of the others is not stated

Hemopoietic Depression Induced by Chloromycetin® Allan Erslev[5] *(Yale Univ)* reports the occurrence of anemia and hypoplasia of the erythropoietic bone marrow tissue in two patients with salmonella infections one of whom had been

(4) J A M A 149 1293 1300 A g 2 1952
(5) Blood 8 1 0 174 F b y 1953

increased Toleration of electrolyte imbalance was greater with increased hemoglobin levels The general expression of increased well being by patients was difficult to evaluate

Dosages in excess of 100 mg a day caused anorexia and eventually nausea and vomiting One patient had persistently loose stools during therapy none had diarrhea Four patients

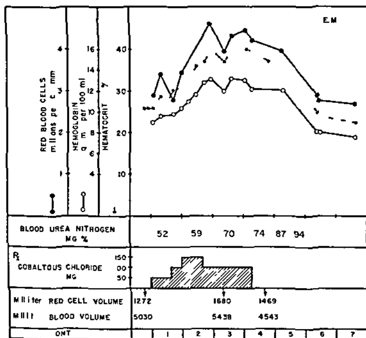


Fig 51 —R po t th py f h on gl merul ph t (C t y f G d F H J Lab & Cl M d 41 56-64 J ry 1953)

noted tinnitus one of these noted severe nerve deafness which began after 12 weeks of therapy but disappeared when therapy was discontinued and returned when it was again initiated There were no cardiovascular complications and no evidence to suggest that cobalt therapy had altered the course of the disease

The direct effect on the kidney parenchyma from prolonged exposure to this metal in low concentration awaits further

suspicion of marrow depression and the drug discontinued if any sign of depression is found With these precautions it seems safe to use this valuable antibiotic when indicated

[Unfortunately disastrous effects apparently due to sensitization have promptly followed the administration of even small amounts of the drug in some patient —Ed]

Use of Cobaltous Chloride in Anemia Associated with Chronic Renal Disease Frank H Gardner[6] (Harvard Med School) reports results of oral administration of cobaltous chloride to 17 patients for four weeks or more This therapeutic program was undertaken because of recent studies and *clinical experiences which suggested that cobalt functions* a a nonspecific erythropoietic stimulant Efforts were made to eliminate repeated blood transfusions determine if subjective improvement occurs with consistently higher hemoglobin levels and evaluate the toxicity of the drug on prolonged administration At first a 50 mg uncoated tablet was used but because of gastrointestinal disturbances a 20 mg enteric coated tablet was substituted Total daily dosage was 50 150 mg and tablets were taken with meals

No significant erythropoietic response could be elicited in less than a four week period of cobalt therapy There was no essential change in the platelet white blood cell or differential counts Reticulocyte response was variable and could not be used to evaluate therapy Most patients showed a significant erythropoietic response in one month as manifested by an increase in red cells hemoglobin content and hematocrit reading Maximal values were reached in two to three months Fourteen patients were followed for 12 weeks after cobalt therapy was discontinued All showed a decline in blood values to pretreatment levels (Fig 51) Indirect measurements of red cell volume with Evans blue did not necessarily correlate with other peripheral blood measurements Four of five patients on whom bone marrow studies were done had distinct increases in erythroid precursors

None of the patients had been treated previously with frequent transfusions No observations were made to demonstrate that these patients had fewer hospital admissions However the increased erythropoietic activity would preclude the need for transfusions Appetites improved and tolerance for the medications necessary to correct electrolyte abnormalities

(6) J Lab & Cl Med 41 56 64 Jan 1953

DIFFERENTIAL FEATURES

	Acute Erythremic Myelosis	Chronic Erythremic Myelosis	Erythroleukemia
Age	Unimportant		
Sex	Unimportant		
Clinical Features			
Fever	Irregular, remittent	Irregular	Irregular
Course	Acute, lasting from few weeks to two months	Chronic, lasting about two years	Acute
Hemorrhagic Manifestations	Prominent	Not prominent	Prominent
Splenomegaly	Considerable	Moderate to marked	Moderate
Hepatomegaly	Moderate	Moderate	Moderate
Hematologic Features			
Red Blood Cells	1.2-1.7 mil u d p pı g t b ut 1 mill t rmı ally Considerable size and shape variation	Moderate anemia progressively increasing. Considerable size and shape variation	Severe anemia
Nucleated RBC	Vary in number, usually primitive, many embryonal forms	Vary in number, usually mature forms	Numerous
White Blood Cells	Usually low, may be normal or high	Usually normal or slightly low	Numerous myeloblasts
Platelets	Diminished	Moderately diminished	Diminished
Reticulocytes	Variable	Usually elevated	Variable
Reticulo-Endothelial Cells	Present in peripheral blood	Not prominent	Not prominent
Marrow	Primitive red cells predominate	Primitive red cells predominate, more old forms present	Proliferation of both primitive red cells and myeloblasts
Pathologic Features	Infiltration of hemopoietic and extra-hemopoietic organs with primitive erythroid and reticulo-endothelial cells	Extramedullary hematopoiesis	Infiltration of hemopoietic and extra-hemopoietic organs with primitive erythroid and myeloid cells

forms The etiology of erythremic myelosis is unknown No sound classification can be made until the cause is known

Di Guglielmo considers the reactivation of the hemato poietic potential of the reticuloendothelial system the initial

study At present it cannot be stated whether renal excretion or retention of cobalt is a toxic hazard to the patient

[These results are of practical importance because hitherto no known therapy other than transfusions or reduction of uremia has been known to elevate circulating hemoglobin values —Ed]

Erythremic Myelosis (Di Guglielmo's Disease) Critical Review with Report of Four Cases, and Comments on Erythroleukemia Steven O Schwartz and Joan Critchlow[7] (Cook County Hosp) report on four women in whom erythremic myelosis lasted from 10 months to 8 years All had low grade fever and loss of weight The cases were characterized by chronic refractory anemia enlargement of the liver and spleen and proliferation in the marrow of young erythroid cells that failed to mature The peripheral blood showed severe hypochromic or normochromic anemia with red blood cell counts generally below 3 000 000 Anisocytosis and poikilocytosis were severe and low reticulocyte counts failed to rise appreciably after liver extract administration There were normal to low white cell counts a differential formula with wide variation but usually showing some degree of monocytosis a left shift in granulocytes with a preponderance of unsegmented forms occasional eosinophilia and depressed platelet count without hemorrhagic manifestations In two cases nucleated red cells occurred in small numbers In the bone marrow highly active erythropoiesis was accompanied by an apparent severe maturation arrest and prominent abnormal red cell forms suggested direct origin from the reticuloendothelium Two cases showed in addition alteration in granulopoiesis with giant band cells and large metamyelocytes reminiscent of those seen in pernicious anemia All the patients died despite treatment with blood transfusions liver extract folic acid and iron preparations Two patients had splenectomy

The disease was first described in Europe particularly in Italy by Di Guglielmo and there has been much confusion as to classification terminology and pathogenesis Di Guglielmo defined the erythremic diseases as specific and primary entities characterized by generalized and systemic proliferations selectively affecting the erythropoietic apparatus According to their course there are acute and chronic forms as well as neoplastic anerythremic and hypoplastic or aplastic

(7) Blood 7 765 793 August 1952

10 850 with 82 polymorphonuclears and 17 lymphocytes Sternal bone marrow showed a moderate degree of hyperplasia of all elements Blood drawn from the femoral artery while the patient was breathing atmospheric air showed 84% oxygen saturation which rose to 91% when oxygen was administered Suboccipital exploration revealed no tumor However thereafter there was more decided slowing of respirations without increase in depth She died 10 days after operation Autopsy showed bilateral cerebellar cystic tumors with internal hydrocephalus and medullary conus The pituitary was normal

CASE 2 —Negro 45 had occipital headaches for six months before hospitalization Later vertigo stumbling gait and blurred vision

BRAIN TUMOR ASSOCIATED WITH POLYCYTHEMIA IN 19 REPORTED CASES

	No C ses
Cerebellar hemangioblastoma	4
Cerebellar angioreticuloma	6
Cerebellar medulloblastoma	1
Frontal lobe endothelioma	1
Cortical subdural hematoma	1
Frontal lobe sarcoma	1
Glioblastoma multiforme	1
Unknown (probably pontile)	1
Unknown	3

Of th 19 11 f m 1 t d 12 w bt t l

developed For three weeks he had had complete deafness in the left ear Physical examination showed a temperature of 98 4 F pulse 100 respiratory rate 6 blood pressure 110/85 Pupillary changes lateral nystagmus with a slow component to the left and bilateral marked papilledema with old and new hemorrhages were found Blood examination showed hemoglobin 17 Gm white count 11 200 with normal differential Sternal marrow examination revealed a normally cellular marrow Blood from the femoral artery had a hemoglobin of 19 Gm with oxygen saturation of 85 4% Suboccipital decompression revealed no tumor Thereafter the patient was given local x ray therapy with gradual improvement of headaches Lateral nystagmus and weakness of the left arm and leg remained but hearing in left ear was improved Femoral arterial blood two months later showed a hemoglobin of 16 5 Gm with an oxygen saturation of 93 7%

The authors point out that only 19 patients with brain tumor and polycythemia have been reported (table) The absence of splenomegaly and of abnormalities of the bone marrow and the definite oxygen unsaturation of the arterial blood samples indicate their patients to have had secondary polycythemia Most other patients have been shown to have subtentorial tumors arising from vascular structures The authors suggest that the relatively slow growth of such tumors may allow for a long survival period associated with depres

and indispensable phase in the pathogenesis of erythremic myelosis He believes that the disease is not primary to the reticuloendothelial system but rather the consequence of a reversion of erythropoiesis to a type of embryonal reticulo endothelial genesis wherever reticulum cells of erythropoietic potential exist An abundance of primitive red cells is then produced Other investigators consider erythremic myelosis a primary disorder of the reticuloendothelial system The authors consider acute and chronic erythremic myelosis and erythroleukemia to be variants of reticuloendotheliosis be cause (1) hyperplasia of the reticuloendothelium was noted in several cases (2) transitional forms between reticulum cells and primitive erythroblasts have been described by Di Gugli elmo (3) frank monocytosis has been present in some cases (4) a disorder of the reticuloendothelium explains the abnor malities in the granulocytes and platelets and (5) it explains the close relationship between cases of erythroleukemia and erythremic myelosis

The differential diagnosis between acute and chronic ery thremic myelosis and erythroleukemia is demonstrated in the table These erythremic diseases must be differentiated from various forms of hemolytic anemia such as Cooley s anemia and erythroblastosis fetalis There is no known treatment for erythremic myelosis and the outcome is usually fatal

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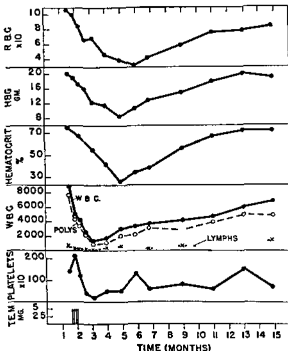
POLYCYTHEMIA

Polycythemia Secondary to Brain Tumor Charles R Holmes Frederick E Kredel and Charles B Hanna[8] (Med College of State of South Carolina) state that a small number of such cases has been reported They present the pertinent findings on two such patients and review the theories con cerning the probable exciting factor

CASE 1—Negro woman 29 complained of headaches for six months then gradually increasing deafness and later increasing blind ness On physical examination she was well developed and nourished temperature being 98 F pulse 84 respiratory rate 10 and blood pressure 106/70 Neurologic examination was consistent with in creased intracranial pressure and meningeal irritation right facial paralysis and bilateral nerve deafness Blood examination revealed red blood cells 6 400 000 hemoglobin 18 3 Gm white blood cells

(8) S th M J 45 967 972 O t be 195

thrombocytes as well as of the erythrocytes provides a more complete picture of the effect of the triethylene melamine on bone marrow Patients in group I showed a relatively marked maximal diminution in red blood cells (45% decrease) white blood cells (76%) and thrombocytes (72%) Patients in group II revealed moderate diminutions in the three elements red



F g 5 —Hem t l g h g ft t thyl m l m tb py (Cou t y t R th l N d R th l R L A M A A h I t M d 90 379 388 S p t mb 1952)

blood cells 21% white blood cells 45% and thrombocytes 54% This indicates that the difference in erythrocyte response between the two groups can be attributed to less over all depression of the bone marrow in group II In group III it not only required a higher dosage of drug to produce a white blood cell and thrombocyte response similar to that in group II but there was a relative lack of erythrocyte response In

sion of the medullary respiratory centers and consequent inadequate respiratory exchange If the polycythemia of brain tumor is due to stimulation of a hypothetical red blood cell *production center* the oxygen saturation of the arterial blood would be expected to be normal as in polycythemia vera

Treatment of Polycythemia Vera with Triethylene Melamine Summary of 30 Cases Nathan Rosenthal (Mount Sinai Hosp New York City) and Robert L Rosenthal[9] (Beth Israel Hosp New York City) administered triethylene melamine to 30 patients with polycythemia vera and followed them for an average of more than one year Triethylene melamine has a nitrogen mustard like action and can be administered orally Like nitrogen mustard and radioactive phosphorus it inhibits the bone marrow and in addition to lowering the red blood cell count causes a reduction in the number of thrombocytes which is increased in over 50% of cases of polycythemia vera Thrombocythemia contributes to both hypercoagulability and abnormal clot formation and retraction which aggravated by the presence of an elevated hematocrit percentage may lead to either intravascular thrombosis or hemorrhage

Triethylene melamine was taken orally one hour before breakfast in dosage of 2 5 or 5 mg every one to three days to a total dose of 15-40 mg Additional dosage was given two to three months later depending on hematologic response There were generally no untoward effects of the drug except for an occasional complaint of nausea

Patients were divided into three groups according to their response to therapy In group I the red blood cell count and hematocrit percentage decreased to normal levels in group II the red blood cell count and hematocrit percentage decreased to values slightly above normal and in group III there was little or no response In groups I and II 20 patients had an average remission of eight to nine months The average age of the patients in group III was higher than that in the other two groups The mean duration of disease from the time of diagnosis to onset of therapy was the shortest in group I Patients in groups I and II generally received one course of the drug averaging 30 35 mg whereas the patients in group III received an average of 59 mg in multiple courses

The analysis of the response of the white blood cells and

(9) A M A Arch Int M d 90 379 388 Sept mb 1952

ment indicated by a significant fall in the hematocrit value Of five patients having symptoms attributed to the disease three had complete relief following therapy and two had decrease in symptoms One patient had nausea and vomiting after the second course and was given no further therapy No other severe toxic reactions were noted In three patients who had hepatosplenomegaly before therapy the liver and spleen were no longer palpable after therapy in two and in the third the spleen but not the liver decreased in size

In all 19 courses were given There was a significant drop in the hematocrit reading after 10 of these courses with an average decrease of 10% There was a fall in the hemoglobin content of 1 Gm /100 cc blood or more after 15 of the 19 courses Decreases in the red cell count ranging from 500 000 to 3 900 000/cu mm occurred after 14 of the 19 courses The lowest white blood cell count observed in any patient was 2 250/cu mm The initial fall in values was noted as early as 14 days after start of therapy and the minimal hematocrit reading occurred 14 70 days after the start of therapy

The results seem sufficiently encouraging to warrant further trial

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LEUKOCYTOSIS AND LEUKOPENIA

Infectious Mononucleosis Value of Differential Absorption Tests in Its Serologic Diagnosis Sidney Leibowitz (Beth Israel Hosp New York City) states that clinical picture hematologic features and hepatic involvement may not be specific enough for diagnosis of infectious mononucleosis The sheep cell agglutination test is necessary to make an accurate diagnosis but it is at times necessary to differentiate the heterophil antibodies by means of absorption tests The percentage of sheep cell agglutination tests with positive results should be high in cases of infectious mononucleosis Sero negative cases are often due to (1) failure to perform agglutination tests early enough in the illness (2) failure to perform repeated agglutination tests late enough in the illness (3) failure to perform confirmatory absorption tests on serum with low titers and (4) failure to exclude cases simulating infectious mononucleosis

( ) Am J Med 13 172 182 A gu t 195

group III patients the erythrocytes and to a lesser degree the white blood cells and thrombocytes were resistant to the drug

In general symptoms disappeared as the red blood cell count and hematocrit percentage fell after therapy The lowest erythrocyte hemoglobin and hematocrit levels were reached in an average of four months after therapy (Fig 52)

The study shows that triethylene melamine has good potentialities in the treatment of polycythemia vera but longer follow up is necessary before its value can be compared with that of radioactive phosphorus The reason for the lack of response of some patients to marrow inhibiting agents is unknown *Older patients with a longer duration of disease and* elevated blood cell and thrombocyte counts are less likely to respond to triethylene melamine Patients with brief duration of the disease minimal previous therapy and normal white blood cell and thrombocyte counts appear to respond better to therapy

The toxicity of triethylene melamine is similar to that of other bone marrow depressants The patient must be closely followed hematologically One patient had transient purpura which occurred coincidentally with thrombocytopenia (20 000 cells) The thrombocyte count fell below 100 000 in 9 of 20 patients in groups I and II after therapy Although triethylene melamine did not produce significant changes in the red blood cell values of patients in group III it did effect a definite decrease in thrombocytes in all seven patients with counts above 400 000

Triethylene Melamine in Polycythemia Vera Therapeutic Trial Rose Ruth Ellison Victor Ginsberg and Janet Watson[1] (State Univ of New York Brooklyn) gave triethylene melamine to six patients (four men) aged 41 70 and followed them for 5 13 months Three had been previously treated with either *HN2* or x ray *The initial course of triethylene melamine* in all six patients was 5 mg daily for four days If no significant decrease in the hematocrit reading occurred in four weeks and white cell depression was not present a second course was given Further dosage was 10 20 mg./course with dose and frequency of administration depending on initial response to therapy

All six patients at some time showed hematologic improve

(1) Cance 6 3 7 33 Ma h 1953

who presents a case Although eosinophilia is characteristic of bronchial asthma a level of over 15% is rare unless there are complications In 1939 Rackemann and Greene directed attention to patients in whom asthma is eventually complicated by extremity pain and numbness and an eosinophil level exceeding 25% They concluded that in such instances periarteritis nodosa is combined with asthma and that the prognosis is poor In a 1945 survey of published cases of periarteritis nodosa Wilson and Alexander found that 18% of the 300 patients also had bronchial asthma average eosinophil level was 53 5% Eosinophil count was increased in only 6% of patients without asthma In 1951 Churg and Strauss reported on 15 patients with bronchial asthma hypereosinophilia and periarteritis nodosa 13 died Hypereosinophilia and polyneuritic symptoms started from a few months to 10 years after onset of asthma which often abated and sometimes disappeared during the terminal illness Duration of the syndrome in the fatal cases was three months to five years Intermittent fever was present in all patients Pneumonia sinusitis renal and cardiac symptoms hypertonia and erythematous and maculopapular skin manifestations were frequent Joints were involved in 4 patients and 10 had peripheral neuropathy Only two patients had a family history of allergy

Girl 17 had had bronchial asthma for 10 months and fever for 2 days before she was hospitalized because of inability to walk and severe aching and tenderness in both legs During a three months stay in the hospital she had no asthmatic symptoms There was transient edema of the legs feet and hands Swollen joints and urticaria like skin manifestations often appeared From midcalf downward the legs were cold and blue and the skin dry and glossy Both soles were anesthetic and there was restricted dorsiflexion of the left ankle and toes of the left foot Leukocytosis and eosinophilia persisted for three month Highest leukocyte count was 55 000 and highest eosinophil level 84 5% Eosinophils were normal in shape and size and bone marrow was normal Clinical diagnosis was eosinophilic leukemia angioneurotic edema acute polyneuritis and bronchial asthma Biopsy which might have proved periarteritis nodosa was not made

The patient has been observed for 6½ years and has been healthy and able to work except when asthma was incapacitating Two years after hospitalization a severe attack of asthma was accompanied by transient pricking and numbness in the feet and swelling of toe joints Eosinophil level rose to 46% at thi time

Inexplicable cases of prolonged eosinophilic hyperleuko

A titer of 1 56 may be considered the upper limit of normal in apparently healthy adults examined by the method of Davidsohn In diseases *other than infectious mononucleosis* and serum sickness heterophil antibody titers above normal levels are occasionally found These are usually of the magnitude of 1 448 or lower The effects of the absorbing antigens (guinea pig kidney and beef erythrocytes) on the heterophil antibodies are different in patients with infectious mononucleosis than in normal persons and in those with other diseases The anti sheep agglutinins in infectious mononucleosis are not *of the Forssman type They are not absorbed by a suspension* of guinea pig kidney The heterophil antibodies in patients with serum sickness and in normal persons are of the Forssman type and are readily absorbed by a suspension of guinea pig kidney The agglutinins are promptly absorbed by boiled beef red corpuscles from the serum of patients with infectious mononucleosis and almost as well from the serum of patients with serum disease but not from normal serum

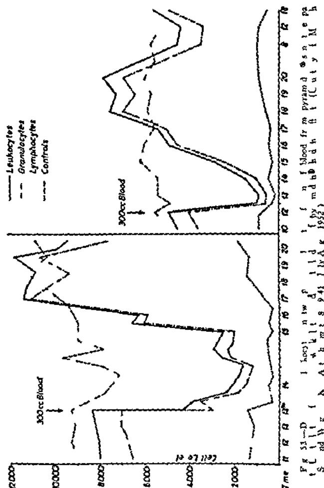
The routine use of the absorption tests as part of the examination of serum for heterophil antibodies is indicated whenever the antibody titer is 1 896 or lower In absence of suspicion of serum sickness a titer of 1 1 792 or higher may for practical purposes be presumed diagnostic of infectious mononucleosis Absorption of the antibodies at any titer is necessary to differentiate serum sickness antibodies from those of infectious mononucleosis The absorption tests are particu*larly informative early during the course of illness when the* titer of the heterophil antibodies show little elevation above normal Without the use of the absorption tests the heterophil antibody test is not specific for infectious mononucleosis

Even in the presence of titers of 1 1 792 and above confirmation by absorption is desirable whenever the possibility of another disease with ominous prognosis enters into consideration or when the case serves as part of a study of *infectious mononucleosis*

[Our difficulty in the diagnosis of infectious mononucleosis in adults has chiefly been the failure to obtain significant titers in unabsorbed positive heterophil tests in a considerable percentage of patients who were clinically affected with glandular fever *and who exhibited atypical* lymphocytes in the blood films —Ed]

Extreme Eosinophilia and Leukocytosis in Connection with Bronchial Asthma *is discussed by* Erkki Klemola[3] (Helsinki)

(3) Acta med sc nd 144 119 123 195



precipitate depletion and exhaustion of the bone marrow due to enormously increased peripheral destruction of the granulocytes rather than by an actual inhibition of the marrow

The length of time that the substance producing the changes remains in the circulation has yet to be determined

cytosis have sometimes been called eosinophilic leukemia This diagnosis has depended on presence of immature cells in the blood and bone marrow and cellular infiltrations Since factors other than leukemia may cause immaturity and cellular infiltrations have been found in patients who died of Rackemann and Greene s syndrome Klemola considers it probable that some cases have not in fact been leukemia

↓ The next article is a most important contribution to the understanding of the pathologic physiology of agranulocytosis The analogy to the observations on drug induced purpura described in a later chapter is seemingly clo e —Ed

Agranulocytosis Due to Occurrence of Leukocyte Agglutinins (Pyramidon® and Cold Agglutinins) S Moeschlin and K Wagner[4] (Univ Clinic Zurich) report that within 20-40 minutes after transfusion of 300 cc blood from a pyramidon® sensitive patient (obtained 3 hours after administration of 0 3 Gm) to two different recipients of the same blood group as the patient a definite granulocytopenia appeared which lasted 3 5 hours (Fig 53) Control transfusions of blood from normal subjects together with ingestion of pyramidon® (0 6 Gm) did not decrease the leukocyte count of these recipients

In vitro it appeared that there is a transferable substance in the plasma and serum of a pyramidon® sensitive patient at the height of agranulocytosis which produces agglutination of homologous and heterologous leukocytes This substance probably protein in nature is produced in response to a pyramidon® hapten The agglutination is probably responsible for removal of the granulocytes from the circulating blood and their destruction most likely in the lungs This process is perhaps the same as that relating to erythrocytes in certain cases of acquired hemolytic anemia The mechanism may also be involved in a whole series of so called anaphylactic agranulocytoses This conclusion was suggested by the appearance of pancytopenia (hemolytic anemia thrombocytopenia and a granulocyte count of 230 in a patient with a cold agglutinin titer of 1 8 000) in association with virus pneumonia Leukopenias occurring in other diseases such as certain rheumatic disorders lupus erythematosus and some forms of hypersplenism may be explained on a similar basis

On the basis of these experimental findings it is believed that changes in the bone marrow are brought about by a

(4) A ta ha m t 8 9 41 July Aug 1952

disappearance of megakaryocytes from the marrow led to demonstration later that blood platelets are derived from megakaryocytes

The clinical significance of the experimental work of Sabin and her associates has largely been neglected and only in sporadic instances has the relation between disseminated tuberculosis and such changes in the peripheral blood as pancytopenia and leukemoid reactions been noticed and reported It is apparent from reports that pancytopenia and leukemoid reactions probably are not the only responses of the peripheral blood and marrow Taken separately these responses appear to have little uniformity but if cases could be followed throughout their courses they would probably fall into a logical sequence parallel to the proliferative and regressive sequences described in the experimental animal

The authors describe a case of pancytopenia in a patient in whom a totally unsuspected disseminated tuberculous process was found at autopsy

Woman 82 had had only minor ailments before hospitalization for increasing weakness of two months duration which had followed a head cold She appeared acutely and chronically ill with evidence of weight loss and pallor her skin was the color of cafe au lait She was restless and confused Temperature was 101 F Blood analysis showed 900 000 red cells hemoglobin 3 4 Gm and 800 white cells with 13 segmented and 7 nonsegmented neutrophils 66 small and 14 large lymphocytes There was poikilocytosis but no macrocytosis Platelets numbered 70 000 Coagulation time was 4 minutes and clot retraction 3½ hours Bone marrow smear was consistent with that of aplastic anemia there were no tubercles in the specimens examined

Blood transfusion (500 cc) was given and 300 000 units of penicillin daily was started On the next day the red cell count was 1 490 000 hemoglobin 4 5 Gm and white cell count 1 450 temperature was 102 6 F A second transfusion was given On the third day temperature rose to 104 6 F and the patient died Anatomic diagnosis after autopsy was disseminated fibrocaseous tuberculosis with tubercles in lung abdominal lymph nodes spleen liver and bone marrow Bone marrow was hypoplastic with replacement by plasma cells and lymphocytes

[The original article emphasi es the variety of clinical appearances of the bone marrow that may be caused by m l ary tuberculosis —Ed]

Chronic Hypoplastic Neutropenia Theodore H Spaet and William Dameshek[6] (Tufts College) present four cases of chronic neutropenia which were nonsplenic noncyclic com

(6) Am J M d 13 35 45 J ly 195

Association of Miliary Tuberculosis of Bone Marrow and Pancytopenia Theodore S Evans Vincent A DeLuca Jr and Levin L Waters[5] (New Haven Conn) review the literature on alterations in the peripheral blood and bone marrow associated with miliary tuberculosis In 1908 Donhauser first related the familiar alterations in peripheral blood in tuberculosis to tuberculosis of the bone marrow In his patient the marrow was hyperplastic and contained many tubercles In 1922 Wiechmann observed numerous tubercles in the bone marrow of two patients who died of tuberculosis and whose blood had shown a leukemoid reaction Dyke in 1924 first called attention to aplastic anemia associated with tuberculosis In one of his cases widespread miliary tuberculosis was proved at autopsy Bacilli were demonstrated in many caseous tubercles in the bone marrow peripheral blood findings during life had been consistent with those of myeloid leukemia

In 1927 Doan and Sabin reported classic experiments on the effect of induced tuberculosis on the blood and bone marrow of animals In all of 80 rabbits inoculated with a bovine strain of tubercle bacilli miliary tuberculous lesions of the bone marrow developed At 8 10 days large numbers of young monocytes began to appear in the marrow at 12 20 days typical epithelioid cells and giant cells of the Langhans type appeared This new tuberculous tissue eliminated much of the marrow fat and encroached on the blood forming foci If the animals survived the first acute reaction the marrow tended to heal spontaneously During and after the third month there was hyperplasia of the blood forming elements Eventually the marrow became normal despite a steadily progressing often fatal tuberculosis elsewhere

Early in the experimental disease peripheral blood showed a sharp fall in platelet count anemia and a fall in number of granulocytes Onset of recovery was marked by return of platelets to normal a rise in hemoglobin concentration followed quickly by a rise in number of red cells and a more gradual increase in number of granulocytes Of especial interest was a definite increase in monocytes associated with a corresponding fall in lymphocyte count This observation has been of clinical aid in following the progression or healing of the disease in man Correlation of a fall in platelet count with

(5) A n I t M d 37 1044 1052 N mb 1952

Corticotrophin and Cortisone in Treatment of Agranulocytosis and Thrombocytopenic Purpura Report of Four Cases Mikko Virkkunen[7] (Helsinki) describes the effects of hormonal therapy on agranulocytosis after thiosemicarbazone therapy in two patients and on thrombocytopenia with purpura after gold salt therapy in two others In both cases of

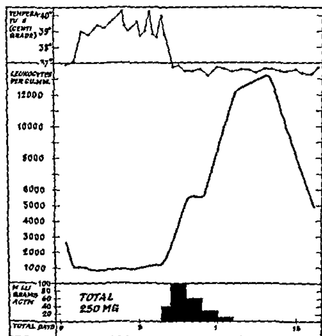


Fig 54 —Effect of corticotrophin on leukocyte count and body temperature in agranulocytosis (Courtesy of Virkkunen M A M A Arch Int Med 90 580 586 November 1952)

agranulocytosis corticotrophin resulted in dramatic response and permanent recovery within two days

CASE 1 —Woman 50 with rheumatoid arthritis was given a total of 7 Gm thiosemicarbazone in five weeks after which she had a fever Leukocyte count was 800 cell /cu mm with 89% lymphocytes 7% monocytes and 4% neutrophil On the sixth day of illness she was given corticotrophin because of mouth lesions and a pericardial friction rub The response to corticotrophin was dramatic

7) A M A Arch Int Med 90 580 586 November 195

pletely obscure as to etiology and apparently due to specific hypoplasia of the marrow granulocytes The condition called chronic hypoplastic neutropenia by the authors has received little attention in the literature Hattersly described one case of chronic neutropenia without primary disease of the marrow in which the neutropenia was unaffected by splenectomy Adams and Witts reported five similar cases in one of which splenectomy was without benefit the remaining four cases showed none of the stigmas of hypersplenism or of other known etiologic factors responsible for neutropenia

All the patients had an extremely chronic course characterized by repeated infections which were relatively resistant to therapy delayed wound healing and paucity of symptoms in the intervals between infections Physical findings were not characteristic except for signs of inflammation of the skin and frequent ulcerative lesions of the mouth Splenomegaly of slight to moderate degree was present in all and with the presence of an extreme degree of neutropenia the possibility of splenic neutropenia was considered The neutropenia showed little variability and great chronicity Absolute lymphocytosis and monocytosis were consistently present and slight anemia and thrombocytopenia were occasionally present Bone marrow aspirations revealed pronounced hypoplasia of the granulocytic precursors in the presence of an otherwise normal cellularity relatively undisturbed erythropoiesis and quantitatively and qualitatively normal megakaryocytes Splenectomy was performed in three cases with no change in the disease Two patients died

Although the disease resembles splenic neutropenia clinically the granulocytic hypoplasia of the marrow and failure to respond to splenectomy are differentiating characteristics Similar cases have been reported in the literature Roberts and Kracke reported on a group of patients showing chronic debility and mild chronic neutropenia with episodes of more severe granulocyte depression occurring at irregular intervals

The pathogenesis of the syndrome is unknown Autopsy and examination of spleens gave no clue as to etiology There seems to be a specific inability of the bone marrow to elaborate granulocytic precursors Provided infections can be controlled the prognosis of the syndrome is compatible with a lengthy course

ment of leukemia occurred when centrifugated or filtered cell free extracts of Ak leukemic organs were inoculated into new born infant mice of the C3H line This happened also when cell suspensions prepared from healthy Ak embryos were so employed

A working hypothesis suggests that mouse leukemia is caused by a transmissible agent that exists in two different forms one is more resistant transmissible filtrable and in active and nonpathogenic for the carrier host the inactive agent may however become activated (oftenest in the middle-aged carrier host) causing rapid multiplication of cells harboring it and resulting in leukemia The activated agent would be fragile and unable to exist except in close association with leukemic cells Under certain experimental conditions the active agent could be transplanted with the leukemic cells into a susceptible host and cause prompt development of leukemic tumors at the site of implantation In cases in which the transplanted leukemic cells although implanted into newborn or susceptible young adult mice would fail to take the inactive agent also present in the cells being more resistant would survive It would remain dormant at first but would be able to cause a delayed development of leukemia

The inactive agent would be transmitted through the embryos from one generation to another and become responsible for the spontaneous development of leukemia in successive generations of certain families of mice

Incidence of Leukemia in Survivors of Atomic Bomb in Hiroshima and Nagasaki, Japan Jarrett H Folley Wayne Borges and Takuso Yamawaki[9] compared incidence and death rate from leukemia for 1948 1949 and 1950 among exposed and nonexposed people of both cities and among persons exposed to radiation at various distances from the hypocenters of the explosions The incidence of leukemia in the exposed populations was significantly higher than in the nonexposed populations of both cities A highly significant increase in incidence of leukemia was found in persons exposed to radiation at distances below as compared to distances beyond 2 000 m Medical histories of the leukemia patients reflected a high incidence of severe radiation injury in those exposed at less than 2 000 m distance

Leukemias in people exposed at less than and over 2 000 m

(9) Am J Med 13 311 3 1 S pt mbe 195

Within 18 hours after three injections of 20 mg each the temperature returned to normal and white cell count rose to 2 500 cells/cu mm Altogether 250 mg corticotrophin was given within four days during which a transitory leukocytosis appeared Then the leukocyte count returned to and remained normal (Fig 54)

CASE 2—Woman 48 with rheumatoid arthritis was given 6 5 Gm thiosemicarbazone within five weeks White cell count was 1 800/cu mm She had fever and tonsillitis She was given 40 mg corticotrophin on the first day and 80 mg on the second leukocyte count promptly rose to 4 000 cells/cu mm and remained normal thereafter [The possibility of spontaneous improvement cannot be excluded Moreover if granulocytopenia has permitted bacterial invasion to begin cortisone therapy might disseminate it Consequently antibacterial chemotherapy such as penicillin and streptomycin should certainly be used —Ed]

The two patients who had thrombocytopenia due to gold salt required more extensive hormonal treatment for permanent remission The delay in recovery may have been due to very slow excretion of gold which made it impossible to inhibit the continuing noxious effects of the drug

[The results of such therapy in purpuras are described in the appropriate chapter by other authors —Ed.]

LEUKEMIAS AND RELATED DISORDERS

The first article in this section is of potential interest beyond the etiology of mouse leukemia Because of the strict experimental conditions that now seem to be necessary for successful transmission of leukemia to an ordinarily unsusceptible strain of mice previous failures to transmit human leukemia to animals may not necessarily continue It is of great interest that filtered cell free extra ts appear to be effective —Ed

Delayed Effects of Inoculation of Ak-Leukemic Cells in Mice of the C3H Line Working Hypothesis on Etiology of Mouse Leukemia Ludwik Gross[8] (V A Hosp Bronx N Y) reports that after inoculation of Ak leukemic cell suspensions into infant mice of either the C3H or of the foster nursed C3H(f) line local leukemic tumors often developed within two to three weeks at the site of inoculation and were promptly followed by generalized leukemia Among mice inoculated in early infancy as well as those inoculated at a more advanced age there were animals which apparently did not initially react to the inoculation They often remained in good health through their middle age In some however generalized leukemia appeared later without evidence of any local neoplasm at the site of the initial inoculation A similar delayed develop

(8) Cance 5 6 0 6 4 May 1952

or recurrent stimulus of the type producing reactive hyper plasia

Study of the histogenesis of follicular lymphoma indicates that the tumor arises from the multipotential mesenchymal cell Although considerable histologic variation may be ob served in lymphosarcoma reticulum cell sarcoma and Hodg kin s disease it is particularly in follicular lymphoma that there are found most of the combinations of tumor type which might be theoretically anticipated in terms of this cell The leukemias Guglielmo s disease and possibly the related group comprising myelofibrosis megakaryocytic hyperplasia and polycythemia vera as well as many of the atypical lymphomas which defy orthodox classification may all be related to the multipotential mesenchymal cell

The initial benign phase of the disease may last a few months or many years and there is nothing to explain the transition to the malignant phase which inevitably follows Once this transition has occurred the course is that of the type of lymphoma which then predominates There is an ex treme degree of histologic variation

Clinically it may be impossible to distinguish follicular lymphoma from other related conditions A history of pro longed and often intermittent enlargement of lymph nodes particularly if general in an otherwise healthy patient sug gests the diagnosis Histologically the lymph nodes may be crammed with enlarged closely packed follicles In some cases the lymph node findings are not specific and the follicles may be widely separated by apparently normal lymphoid tissue Other variations from the characteristic pattern may occur In such cases it seems better not to use the term reactive hyper plasia but to report the appearances and indicate the possibili ties The presence or absence of intrafollicular reticulin fibrils incidence of mitotic figures and capsular infiltration stressed by some authors have in the authors experience been of lit tle differential value Reticulin stains are worth using but are not specific Histologically the transition stages are readily apparent when the clinical change has occurred but in the uncomplicated early phase there seems to be no reliable cri teria for determining the imminence of transition though oc casionally a striking proliferation of reticulum cells may indi cate the direction in which ultimate differentiation will occur

distance were commonest among early and intermediate age groups Acute and myelocytic leukemias have predominated regardless of the victim's distance from the hypocenter Chronic lymphatic leukemia was found in only one case

The number of cases was small and the types of leukemia not inconsistent with the age distribution in which they occurred Comparative differences in the sex distribution were slight and the total numbers too small to warrant any conclusions on the possible effect of irradiation exposure in accelerating the natural development of leukemia or in determining its type

[These conclusions are consistent with the suggestive statistical evidence concerning the greater incidence of leukemia in radiologists than in other members of the medical profession Here too the condition appears only after many years of exposure —Ed]

Follicular Lymphoma G Wetherley Mein P Smith M R Geake and H J Anderson[1] (St Thomas s Hosp London) review 208 previously reported cases and add data on 29 new cases In 1939 Mayer and Thomas suggested that the disease exists in two different phases The first is relatively benign as the patient is not ill and is characterized by local or general lymph node enlargement with or without splenomegaly and maintenance of the typical follicular pattern histologically The second or malignant phase is characterized by weight loss fever dyspnea and edema and the patient is ill Examination may reveal anemia ascites pleural effusions and signs of bone and visceral involvement Histologically there is evidence of complete or partial transition to some form of malignant lymphoma

From the reported cases it is evident that at a certain stage if not from the outset this disease is frankly neoplastic However there are features which justify a consideration of its possible relation to inflammatory processes The histologic appearances in the early phase may closely resemble those of reactive hyperplasia and it is not uncommon for the initial lymphadenopathy to be associated with some local or general inflammatory process The occasional prolongation of the early phase for many years with a fluctuating or intermittent lymphadenopathy suggests that initially this may be an inflammatory process in which as stated by Scott and Robb Smith the lymphoid tissue is goaded into neoplasia by a prolonged

(1) Q J Med 21 3 7 351 July 1952

This is common in the ribs ischium and upper femur Osteo lytic bone lesions also appear as trabeculated cystic tumors Their roentgen appearance is that of a soap bubble This type of lesion is encountered in the sternum and clavicle The most frequent sites of osseous involvement by myeloma are the skull ribs spine and pelvis Recalcification of lesions is seldom seen after radiation therapy None of the described roentgen features is specific for plasmocytoma

Bone involvement in lymphosarcoma is rare and of terminal nature occurring in 7 10% of all cases The roentgen appear ance is similar to that of plasmocytoma with punched-ou areas and osteoporosis Trabeculated cystic areas sclerotic changes (osteoplastic metastases) and periosteal reactions oc cur also Pathologic fractures are encountered The common est sites of bone involvement by lymphosarcoma are the ribs spine and femur

In osteomyelosclerosis roentgen examination shows a marked increase in the number and thickness of the bone trabeculae and areas of mottling and rarefaction (hypertrophic atrophy) Isolated and scattered condensation areas are in clined to confluence to such a degree that it may be difficult to distinguish bone structure The commonest sites of osteo sclerosis are the vertebral bodies sternum ribs pelvis prox imal regions of humerus femur and tibia and the distal region of the femur The skull is not regularly involved Either spotted sclerosis of the skull vault or diffuse condensation may be found Small bones of the hands and feet are seldom in volved Roentgenographically osteomyelosclerosis resembles many diseases

[The original article co ita ns 15 excellent reproduct o s of ro ntgeno gram —Ed]

Observations on Peripheral Blood in Reticulosarcoma F da Silva Parreira and E Salvidio[3] (Siena) report the dis covery of binuclear cells in peripheral blood of seven patients with reticulosarcoma The 7 cc specimens of blood from cubital veins were heparinized and allowed to stand in test tubes for half an hour Then the supernatant plasma was care fully withdrawn with a pipet and centrifuged very slowly for a few minutes A small amount was kept for slides which were stained by the May Grunwald Giemsa technic The specimens showed monocytosis and hypersegmentation The monocytes

(3) H m tol g 37 05 715 195

Follicular lymphoma is fatal It is impossible to forecast expectation of life and difficult to assess any treatment In the benign phase follicular lymphoma is extremely radiosensitive and the tumors often appear to resolve completely with radio therapy There is no evidence that this treatment accelerates or precipitates transition to the malignant phase but it cannot be proved that it prolongs life In the malignant phase the response to radiotherapy varies with the type of tumor which is developing and in most cases a sudden or gradual decrease in sensitivity becomes apparent when transition to this phase occurs Excision of an isolated tumor may be necessary for diagnosis or for cosmetic or physical reasons

Skeletal Changes in Myelomatosis, Lymphosarcoma and Osteomyelosclerosis are described by Umberto Cocchi[2] (Univ of Zurich) Anatomically three types of myelomatosis can be distinguished (1) diffuse infiltration starting from a localized growth (plasmocytosis) and considered the precocious form of the disease (2) multinodular growth following diffuse infiltration often combined with the first type and (3) a solitary form of single bone tumor The first and third types are rare and generally pass over to the second

Roentgenologically two main types of lesions occur diffuse osteoporosis or osteolytic lesions Purely diffuse osteoporosis is rare and can occur in almost the whole osseous system It is often the antecedent of the second type and represents diffuse plasma cell infiltration Instead of uniform porosis coarsely thickened bone structure (hypertrophic atrophy) may be seen The osteolytic bone lesions are oval or rounded more or less sharply limited punched out transparent areas varying from millet seed to apple size They can appear as a single focus or as multiple foci all without sclerotic reactions Generally the multiple bone lesions are associated with osteoporosis Pathologic fractures occur most frequently in these areas—in about 40-60% of all cases—especially in the vertebrae ribs long bones and clavicles Often in the spine the plasma cell growths destroy the bone outlines producing pathologic fractures of the vertebrae and resulting in wedge shaped and flattened vertebrae The small vertebral joints always remain intact Spread of bone destruction is progressive Sometimes the affected bones are completely invaded and the cortex extremely thinned by tumor

(2) Am J Roentg of 68 370 583 Octobe 1952

detect them in normal blood and in the blood of patients with other blood diseases were unsuccessful They seem therefore to have some diagnostic value and their significance is being studied

Leukemic Myelomatosis (Plasma Cell Leukemia) Review with Report of Four Cases is presented by Jorgen Bichel Poul Effersøe Harald Gormesen and Niels Harboe[4] (Copenhagen) Only cases with 20% or more plasma cells in the peripheral blood are considered

From Jan 1 1943 to Dec 31 1947 four cases of plasma cell leukemia were reported to the Danish cancer registry Including 37 cases from the literature 19 were in men and 21 in women (sex not mentioned in 1) aged 25 80 most of them between 60 and 79 The disease lasted less than 1 month to as long as 24 months average 6 months There was no distinct correlation between duration and age The ratio of nonleukemic myelomatosis (multiple myeloma) to leukemic myelomatosis (plasma cell leukemia) was 50 1 and of myelogenous plus lymphatic leukemias to plasma cell leukemia 250 1

Lassitude weakness weight loss and progressive anemia are the main symptoms often with a hemorrhagic tendency particularly from nose and gingiva Skin hemorrhages are fairly rare Vague bone pain may be present but is not often encountered in the acute and subacute cases Bone pain pre dominated in the chronic cases The liver was enlarged in 18 of 34 cases the spleen in 33 of 37 cases and the lymph nodes in 17 of 26 cases Osteoporosis and focal bone destruction were observed on x rays of about half the patients examined

Moderate to severe hypochromic anemia is a constant find ing Total maximal leukocyte count ranged from 5 000 10 000 to 175 000/cu mm with most values between 11 000 and 40 000 The total count usually rises as the disease progresses The percentage of plasma cells varied from 20 to 99% but less than half the patients had counts over 50% There is a distinct increase in number of plasma cells in the peripheral blood as the disease progresses In a large number of cases the cells are markedly atypical and of immature myeloma cell type suggesting that myeloma with a slightly differentiated cell type becomes leukemic more often than myeloma with more differentiated cell types Relative neutropenia some im

(4) Acta d 1 37 196 207 M Ap 1952

presented nuclear deformities polymorphism and a tendency to segmentation but there were no frankly atypical forms or clear indications of profound immaturity Although the significance of the monocytosis in these patients should be considered in connection with all of the histopathologic findings it occurred even in a patient whose tumor was circumscribed and limited to the axillary glands alone and in whom no signs of systemic involvement were found even at autopsy (Fig 55)

This report calls attention to discovery of binuclear cells



Fig 55 —B nucl blood ells n pat nt w th t cul r oma (Court y of P sa F da S nd Sal d E H em t l g a 37 705 715 1952)

which are not known to occur in other forms of aleukemic disease The cells ranged from the size of a granulocyte to that of a large monocyte the larger ones predominating slightly Cytoplasm was uniform fairly compact and susceptible to weak and medium staining The two nuclei might be equal or unequal in size and while sometimes round usually were oval but slightly flattened on the adjacent surfaces The chromatin structure mostly very dense did not permit identification of a clear reticular framework and often showed areas of conspicuous chromatinic thickening Only a few of these elements presented a fine monocytoid reticulum and nucleoli The binuclear cells may belong to the histiomonocytic series Efforts to

capable of detecting the protein in concentrations less than 0 1 Gm /100 cc

A technic is described in which the addition of Freund s adjuvant to precipitated purified lyophilized Bence Jones protein obtained from six patients with known multiple myeloma induced sufficient immune response in rabbits to make the antiserum suitable for clinical tests A maximal precipitin titer of 1 1 050 was obtained Both the homologous and the heterologous antigen antibody titrations were high in all specimens

The demonstration of cross precipitin reactions rendered the high titered antiserums of value in diagnosis A simple precipitin test for Bence Jones protein utilizing patients urine and antiserums prepared by the adjuvant technic was instituted and carried out in 1 000 subjects Results were positive in 57 53 of whom had multiple myeloma Bence Jones protein had been detected in the urine by chemical tests in only 11 In 33 cases the diagnosis of multiple myeloma was not made before the demonstration of Bence Jones protein by the precipitin test Negative chemical test results and positive serologic results were found in three patients in whom subsequent laparotomies disclosed so called solitary plasmacytomas A negative chemical test result with positive serologic result was found in one case of acute lymphatic leukemia

The consistent demonstration of cross precipitin reactions in heterologous antigen antibody reactions points to antigenic similarity of the six proteins used and warrants the use of the antiserum in clinical diagnosis Absence of false positive reactions failure to precipitate normal human gamma globulin with the antiserums and failure to precipitate the purified Bence Jones protein with antihuman gamma globulin serum are interpreted as showing the antigenic specificity of the proteins studied and the value of the test

Antiserum prepared by the adjuvant modification of immunization of Bence Jones protein was employed in testing for redissolved crystalline Bence Jones protein prepared by serial dilutions Positive results of precipitin tests were found in dilutions as great as 0 007 Gm /100 cc

Thyrotoxicosis with Features Simulating Lymphoblastoma Robert C Levy and Herbert G Levin[6] (Michael Reese Hosp) *report a case*

(6) A I t M d 35 1371 13 3 D mbe 1951

mature granulocytes and erythroblasts may also be seen Thrombocyte counts of about 50 000/cu mm are almost constant

Proteinuria and Bence Jones proteinuria occur with equal frequency in leukemic and aleukemic myeloma The serum proteins seem to behave similarly in both plasma cell leukemia and myelomatosis

In all cases bone marrow examination revealed either massive diffuse or both diffuse and focal infiltration by plasma cells In general liver and splenic enlargement was only moderate In almost all patients examined both organs were infiltrated by plasma cells as were the lymph nodes Infiltration of the kidney as well as of other organs was common

Effective therapy is unknown Roentgen treatment reduces the number of leukemic cells in the peripheral blood and relieves pain

All transitional forms seem to exist between aleukemic subleukemic and leukemic myelomatosis with or without circumscribed bone foci and with or without infiltrations of other organs It seems natural to regard these conditions as different manifestations of the same osseous plasma cell neoplasia (myelomatosis or multiple myeloma) Even though some cases of acute or subacute myelomatosis may actually conform with the concept of leukemia it seems more consistent to designate them as leukemic myelomatosis rather than plasma cell leukemia Theoretically it is possible that a plasma cell leukemia might arise from lymphatic tissue and remain extramedullary

Precipitin Test for Bence Jones Protein Further Studies of Clinical Evaluation of Test Employing Antibody Prepared by Adjuvant Technic Fred C Collier and Paul Jackson[5] (Bowman Gray School of Medicine) state that a valuable aid for earlier diagnosis of multiple myeloma is a precipitin test capable of detecting Bence Jones protein in the urine at an early stage when its concentration is relatively low It is probable that Bence Jones protein is found in the urine by chemical tests in about half the patients with multiple myeloma This relative infrequency of the finding by chemical tests is a result of the inadequacy of the tests rather than the rarity of the protein since even the best of these tests is in

(5) New England J Med 248 409 414 M 5 1953

three Negroes and most of the patients were boys of pre school age Symptoms and signs in the preschool child were often the same as those in disease of the upper respiratory tract or consisted of pallor anorexia pain in the extremities or lymphadenopathy Some had abdominal pain and distention diarrheal stools and headaches Age could not be correlated with symptoms Diagnosis in approximately two thirds of the patients could be based on the peripheral smear Many pa tients especially in the terminal stages had hemorrhagic manifestations Patients in both groups were given blood transfusions as supportive therapy when indicated Because the patients withstood infection poorly antibiotic therapy was often necessary for both groups despite folic acid antago nists

The interval between initial symptoms and diagnosis in group A was four months and in group B two months The mean duration of life after initial symptoms was 5 45 months in group A and 13 3 months in group B Age and survival time were not correlated

Aminopterin therapy began with 1 mg administered par enterally for two days and continued with 0 5 mg orally each day thereafter until a remission in the marrow was noted or until a change to the less toxic (but less effective) a methop terin was deemed advisable All patients received the same dosage Some patients showed no signs of toxicity for as long as six to eight months Bone marrow aspirations were done at biweekly intervals until a remission occurred and at monthly intervals thereafter A methopterin was given in 5 mg doses The patients who showed bone marrow remission converted to a normal marrow at a mean of 8 9 weeks Antagonist therapy should be continued throughout the disease under carefully controlled conditions Actual bone marrow remission persisted for an average of 9 4 months in 12 patients In group B the mean duration of illness was 15 months and the length of therapy 11 9 months

The study shows that aminopterin can prolong life in chil dren who have acute leukemia With prolongation there is clinical improvement Medication should begin as early in the disease as possible Citrovorum factor has helped to heal aminopterin induced lesions of the oral mucosa but also prob ably neutralizes the beneficial effect of anti folic therapy on the leukemic process

Man 34 during the year preceding hospitalization had lost 15 lb A month before admission he began to vomit daily A week later diarrhea developed and two weeks before admission he had a sharp pain in the right upper quadrant and noted protrusion of the upper abdomen Tremor of the right hand was noted occasionally The protrusion increased and pain became more intense On examination the patient appeared acutely ill Blood pressure was 120/80 and pulse rate 120 The thyroid was slightly enlarged generally The heart was enlarged with a pronounced apical thrust and the heart rhythm was totally irregular The liver was greatly enlarged and tender and extended down to the level of the umbilicus The spleen was not palpable The cervical axillary epitrochlear and inguinal lymph nodes were enlarged hard and tender There was increased distention of the cervical veins on the right side dulness over the sternum on percussion and complete absence of any peripheral or sacral edema An initial diagnosis of lymphoblastoma with mediastinal involvement was made

Venous pressure and circulation time studies revealed that the liver was enlarged as a result of congestion The auricular fibrillation and tachycardia enlarged thyroid restlessness of the patient and history of weight loss indicated a diagnosis of primary hyperthyroidism with cardiac involvement and congestive failure The BMR was + 37% and + 44% on two occasions Blood counts and morphology were not remarkable Biopsy of an axillary lymph node showed benign follicular hyperplasia

The patient received mercuhydrin® digitoxin and Lugol s solution with striking amelioration of symptoms Twenty three days after starting Lugol s solution the patient underwent subtotal thyroidectomy Recovery was uneventful and a few weeks after surgery there was no residual lymphadenopathy

Even though the relation between the thyroid gland and the lymphatic organs has been recognized for a long time the mechanism of this relation is not yet understood It is possible that the pronounced degree of hyperthyroidism in this patient may have led to a state of adrenal cortical exhaustion with resulting lymphadenopathy

[Although the differential white cell count was not reported as unusual in this patient in others relative lymphocytosis may be present with atypical lymphocytes These findings further suggest the erroneous diagnosis of lymphoblastoma —Ed]

Treatment of Acute Leukemia in Children with and without Folic Acid Antagonists H G Poncher H A Waisman J B Richmond O \ Horak and L R Limarzi[7] (Univ of Illinois) compare 48 acute leukemia patients (group A) studied in the past 20 years with 38 who were treated with folic acid antagonists (group B) in 1948 51 Altogether there were only

(7) J P d t 41 377 394 O t be 195

three Negroes and most of the patients were boys of pre school age Symptoms and signs in the preschool child were often the same as those in disease of the upper respiratory tract or consisted of pallor anorexia pain in the extremities or lymphadenopathy Some had abdominal pain and distention diarrheal stools and headaches Age could not be correlated with symptoms Diagnosis in approximately two thirds of the patients could be based on the peripheral smear Many pa tients especially in the terminal stages had hemorrhagic manifestations Patients in both groups were given blood transfusions as supportive therapy when indicated Because the patients withstood infection poorly antibiotic therapy was often necessary for both groups despite folic acid antago nists

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The precise mode of action of folic acid antagonists has not yet been defined They act either to prevent undue accumulation of folic acid or the citrovorum factor within the early cell forms or to allow normal maturation processes which act through still other enzymes to proceed

Triethylene Melamine in Treatment of Neoplastic Disease R Wayne Rundles and W Bruce Barton[8] (Duke Univ) report data on 134 patients with various neoplastic diseases treated with triethylene melamine (TEM) orally over 18 months The effect of this drug on normal and neoplastic tissues appears to be identical with that of the nitrogen mustard compounds which inhibit cell mitosis produce cytologic alterations distort cell function and may even cause cell death The tissues predominantly affected are those in which there is active cellular proliferation particularly the lymphoid tissues and bone marrow The effectiveness of TEM given orally and its relative freedom from disturbing side reactions in contrast to nitrogen mustard make optimally spaced and sustained therapy feasible The generalized action of the drug renders it suitable for treatment of diseases which involve tissues in widespread anatomic areas

Triethylene melamine was found to be an important addition to the chemotherapeutic agents useful in malignant disease particularly Hodgkin s disease malignant lymphoma chronic lymphocytic leukemia lymphoepithelioma of the nasopharynx and papillary cystadenocarcinoma of the ovary

Of 25 patients with Hodgkin s disease treated with TEM 9 had excellent 5 good 4 slight and 7 inconclusive results as regards fever weakness lymph node enlargement pruritus and anemia Supplementary roentgen therapy was given to those with persistent local lesions The good or excellent results occurred characteristically in the patients who had had no previous treatment or who had fresh lesions after earlier roentgen therapy The patients with poor results had widespread disease Patients with localized disease are best treated with radiation Those with disease in many areas may respond well if they are first treated with TEM over weeks or months until maximal improvement has occurred Residual areas of disease should then be irradiated

Twenty patients with malignant lymphomas (follicular lymphocytic and lymphoblastic lymphoma and reticulum cell

(8) Blood 7 483 507 M y 1952

sarcoma) and widespread lymph node involvement were treated with TEM Abnormal leukocytes were not present in the circulating blood As judged largely by reduction in size of the local tumors results were excellent in seven good in three slight in five and inconclusive in two Three were not benefited The good to excellent results occurred in patients with newly developed tumors some of whom had been previously treated successfully with radiation and in those given TEM initially Poor results were obtained in patients with rapidly extending or recurring disease Bulky tumors usually respond well to local irradiation but when there is widespread involvement of lymphoid tissue TEM should be used

Of 23 patients with chronic lymphocytic leukemia and high leukocyte counts given TEM 12 had excellent results although in 2 pre existing anemia due to bone marrow replacement was never overcome Six had good results but two remained anemic and five showed slight improvement In those with poor results the leukemic process was advancing rapidly Development of anemia or thrombocytopenia or both indications of bone marrow involvement is the most serious complication of chronic lymphatic leukemia Neither irradiation nor radioactive phosphorus can be effective if the bone marrow is already involved In such a case the beneficial effect of TEM appears to surpass that of any other agent

Sixteen patients with chronic subleukemic lymphocytic leukemia all with a normal or low leukocyte count were treated with excellent response in four and slight in seven Three showed no response and results were inconclusive in two There was a high incidence of bone marrow replacement Three patients with acute lymphocytic leukemia seven with acute granulocytic leukemia and three with multiple myeloma had uniformly poor results Of six with chronic granulocytic leukemia four showed a good and two a slight response Three with polycythemia vera showed variable responses

Of 22 patients with widespread tumors not primarily of hemopoietic origin all except those with lymphoepitheliomas arising from the nasopharynx and those with papillary cyst adenocarcinoma of the ovary showed a poor response to treatment

The critical problem in TEM therapy is administration of therapeutically adequate amounts of the chemical with avoidance of the serious hazards of overdosage The effective oral

dose varies greatly from patient to patient With adequate precautions TEM can be used without undue risk It is well suited for sustained therapy without production of cumulative damage to normal tissues The effective total dose during the first one to three weeks of treatment averages 15 25 mg Some patients will have depression of bone marrow function with a smaller dose and others can take as much as 15 mg weekly almost indefinitely The considerable variation in effective dose for different patients does not appear related to the type of disease present Smaller doses should be used in those with pre existing bone marrow damage The initial oral dose should not exceed 2 5 mg If this is well tolerated for one or two days the dose may be increased to 5 mg The white blood cell count should be determined before each dose is given The full effect of a given dose may not be manifest for 10 14 days Anemia or thrombocytopenia rarely develops without antecedent depression of marrow function

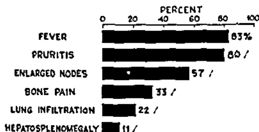
The action of TEM is transitory and there is always the problem of maintaining a therapeutic effect and preventing relapses The drug can be used for long periods at intervals no greater than one to two weeks Prolonged remission has been maintained with doses as small as 1 25 mg/week whereas other patients need 5 mg twice a week Although the period of administration for maximal long term results has not been determined treatment should be sustained for at least five to six months even though signs of disease activity may disappear sooner Many patients will need TEM indefinitely Deleterious effects from sustained therapy other than temporary depression of bone marrow function have not been observed The chief value of TEM is its ability to suppress the objective manifestations of some diseases continuously even in the absence of clinical symptoms and to prevent if possible development of complications such as bone marrow damage

Clinical Use of Triethylene Melamine Sheldon C Kravitz Henry D Diamond and Lloyd F Craver[9] (Memorial Cancer Center New York City) report results in 64 patients with neoplastic conditions mostly malignant lymphomas treated with triethylene melamine (TEM) orally or intravenously The oral dose was 2 5 or 5 mg daily until 10 15 mg had been given to patients with Hodgkin s disease reticulum cell sar

(9) Blood 7 7 974 July 195

coma and chronic myelocytic leukemia and 5 10 mg to patients with lymphosarcoma and chronic lymphocytic leukemia Further medication depended on the patient s progress and was usually 5 10 mg weekly Experience showed the average total oral dose necessary for remission to be 35 mg For intravenous therapy 3 mg was given on two successive days followed by 3 mg 7 10 days later if symptoms continued and no leukopenia had been produced An adequate course of TEM given in this manner was usually 9 12 mg

Patients with Hodgkin s disease were divided into four categories I patients (2) who had received no previous ther



Fg 56—R po f ympt m d g f H dgk n d t TEM (C rt y f K t S C t l Blood 7 729 74 J ly 1952)

apy II patients (6) in good general condition with few objective signs of the disease III patients (18) with widespread disease and constitutional ymptoms but still in fairly good condition and IV patients (10) with widespread disease and constitutional symptoms but in poor general condition The two patients in category I both young had satisfactory remissions In the other three categories good responses were obtained initially in almost all patients improvement lasting one to six months When relapse occurred further remission could be obtained with TEM with considerable palliation The differences in response of the various manifestations of Hodgkin s disease are summarized in Figure 56 Response to TEM depends on the amount of active disease and the patient s general condition Patients with slight lymphadenopathy and fever sweats and pruritus do well Those with bulky nodes lung and bone infiltration and severe hepatosplenomegaly do not respond as satisfactorily Partial response however is occasionally obtained in far advanced cases

Results of TEM therapy in seven patients with lymphosarcoma were poor Only one patient had a prolonged remission The drug was given to five patients with reticulum cell sarcoma and all died of the disease All had generalized lymphadenopathy and were in the terminal stage when treated Of eight patients with chronic myelocytic leukemia given TEM four died The four living patients showed symptomatic improvement and lowering of the white blood cell count and in two the size of the spleen decreased Two of the patients who died had shown some improvement in the white blood cell count One patient with chronic lymphocytic leukemia was treated with TEM with improvement in the white blood cell count He had no depression of the bone marrow although he was receiving 15 mg weekly One patient with Boeck s sarcoid one with extensive mycosis fungoides and five with far advanced bronchogenic carcinoma were treated with TEM with poor results except in two patients with carcinoma These two who were living two years after onset of symptoms had also received x ray therapy

In chronic leukemias TEM appears to be effective for palliation It should not be used in the early stages of myelocytic leukemia since x ray therapy or radioactive phosphorus will give excellent results It should be given when x ray therapy is no longer effective

Therapeutic results with TEM and HN2 are parallel TEM is more useful because it can be given orally and has less gastric effects Serious toxic manifestations of TEM therapy are bone marrow depression and production of hyperuricemia followed by uremia Leukopenia however is not a contraindication to use of this drug

TEM is not the agent of choice in the initial treatment of the usual patient with malignant lymphoma Patients with Hodgkin s disease or lymphosarcoma whose disease is confined to one locus or one region of the body are best treated with x rays locally When palliative treatment of generalized disease is desired TEM may be used For the chronic leukemias TEM may be added to the armamentarium of agents which include urethane Fowler s solution radioactive phosphorus and other general cell poisons Patients may be maintained on small oral doses of TEM for long periods but extreme caution must be exercised since tolerance varies considerably with each patient

Triethylene Melamine in Human Malignant Disease Results with Oral Administration of Enteric Coated Tablets Triethylene melamine (TEM) has produced inconsistent results when given orally Because it is unstable to acids it seemed likely to Edith Paterson P B Kunkler and A L Walpole[1] (Manchester) that the erratic response was due to variable inactivation of the drug in the stomach After experiments with dogs proved that enteric coated tablets produced much more consistent results than plain tablets or gelatin capsules they were given to 44 patients 1 of whom was moribund on admission and died the day after treatment All cases were advanced and in most irradiation could not be used or response to irradiation urethane nitrogen mustard and TEM given intravenously had ceased

Twenty two patients had Hodgkin s disease The usual dose was about 0 3 mg /kg given either undivided or spread over two or three days Symptomatic remissions of eight weeks or more were obtained in 12 patients The general condition improved in all but five patients In most patients enlarged lymph nodes decreased in size spleen size decreased in four Itching and pain especially that from spinal deposits were relieved Leukopenia occurred in 13 patients and was serious in 6 After a study of these cases the authors concluded that TEM should not be given to a patient with a low initial polymorphonuclear count and that a single dose of 0 3 mg /kg should not be exceeded a slight reduction might be advantageous No advantage was found in spreading the dose over several days Treatment may be repeated provided the polymorphonuclear count is fully restored Most patients were hospitalized outpatients reported weekly for a blood count and were hospitalized if the white cell count became unsatisfactory In general results of orally administered TEM in Hodgkin s disease closely resembled those obtained by intravenous injection and those achieved with the nitrogen mustards

TEM tablets were given to 14 patients with chronic leukemia The dose was 0 1 0 2 mg /kg given at intervals determined by response but not less than 14 days Satisfactory remissions of four to eight months were obtained in five of seven patients with lymphoid leukemia in four spleen size was reduced and in three the nodes became smaller No attempt was made to keep the white cell count within normal limits

(1) Brit M J 1 59 64 J 10 1953

Erythropoiesis was not adversely affected and hemoglobin levels increased Five of seven patients with myeloid leukemia died, all had advanced cases and had been treated with x rays urethane or both Two patients who had had no previous treatment had remissions of five and six months It is encouraging that lymphoid leukemia responded better than myeloid because with other agents the reverse has generally been true

TEM orally benefited two patients with reticuloendothelial disease but had no effect on two with carcinoma of the breast two others with radioresistant tumors and one with polycythemia vera

The authors conclude that oral administration of TEM in enteric coated tablets is worth while but they caution against its use without essential hematologic control Their results corroborate previous reports on the value of TEM when used intravenously for neoplasms of the reticuloendothelial system

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HYPERSPLENISM

Hypersplenism is conceived to be the effect of a hyperactive and frequently hypertrophied spleen either by inhibition of bone marrow activity or by acceleration of the destruction of the morphologic elements of the blood It is doubtful that hypersplenism is a primary splenic process Much evidence suggests that it is secondary to a variety of causes of splenomegaly The first article is perhaps the first successful attempt to produce secondary hypersplenism by nonspecific means —Ed

Experimental Production of Splenomegaly, Anemia and Leukopenia in Albino Rats The association of splenomegaly with a decrease in one or more of the formed elements of the blood is frequent in various diseases Splenectomy often alleviates the hemopoietic abnormalities although the underlying disease remains unaltered Such hemopoietic disorders have been called secondary hypersplenism but the manner in which the spleen is related to them is uncertain

Because earlier experiments [1951 Year Book p 333 —Ed] showed that leukocytosis followed splenectomy in the rat J G Palmer E J Eichwald G E Cartwright and M M Wintrobe (Univ of Utah) performed experiments to determine whether splenomegaly in the rat would be associated with leukopenia Splenomegaly was produced by repeated in

(2) Blood 8 72 80 January 1953

jection of methyl cellulose Four groups of rats were studied Group 1 rats served as control group 2 received methyl cellulose group 3 had splenectomy and methyl cellulose and group 4 had only splenectomy After 15 weeks the animals were killed

The spleens of all group 2 animals were massively enlarged and whitish gray areas were frequently seen on the surface Microscopically about one third of the red pulp was taken up by clusters of macrophages many containing a few lymphocytes and reticulum cells There was diffuse hyperplasia of the reticulum of the red pulp Storage of hemosiderin was absent *In the bone marrows of rats given methyl cellulose* (groups 2 and 3) there were increased cellularity depletion of fat cells in marrow cavities and increased hemopoietic elements Livers of these rats showed a scattering of storage cell clusters and granulomas Kidney changes were pronounced Most glomeruli were enlarged and contained numerous storage cells the capillary bed was obliterated There were moderate to severe degenerative changes in the epithelium of many tubules The cortical stroma contained occasional bands or clusters of storage cells and was irregularly infiltrated with inflammatory cells

Leukopenia was found in group 2 animals only it was severe and almost entirely due to reduction in number of mononuclear cells Hemoglobin concentration was reduced but because of a parallel decrease in erythrocyte count and volume of packed red cells red cell indexes showed little change Hemoglobin concentration was decreased in splenectomized animals also but to less degree Reticulocytosis was striking in group 2 animals but was not seen in the other groups Serum bilirubin could not be detected in any of the animals Platelet counts were lowest in group 2 and highest in group 3 Differential counts on marrow smears showed no significant differences in the four groups

The syndrome produced by methyl cellulose may represent an experimental form of the clinical process called secondary hypersplenism in man Characteristic of both are splenomegaly hyperplasia of bone marrow normocytic normochromic anemia and leukopenia In man the disorder is often but not always associated with thrombocytopenia mild thrombocytopenia was observed in 90% of the rats

The experiments demonstrate a relation between presence or absence of the spleen and reduction in blood cellular elements but they do not explain the pathogenesis of these changes The finding of a normocytic normochromic anemia with reticulocytosis suggests that hemolysis may play a role Absence of bilirubinemia does not eliminate this possibility because of the ease with which large amounts of bilirubin are cleared from the plasma in rats The possibility that blood changes were due to impaired renal function seems unlikely because these changes did not occur in splenectomized animals and there was no nitrogen retention

[It is of interest that according to Janet Watson in patients with sickle cell anemia and splenomegaly the survival time of transfused normal red cells is reduced whereas it is normal in such patients without enlarged spleens or with atrophied spleens The masses of trapped sickled red cells in the enlarged spleens of these patients as well as the diverse causes of splenomegaly that clinically result in hemolytic anemia and now the completely foreign character of the methyl cellulose suggest the nonspecificity of the splenomegaly of the hypersplenic syndrome The characteristics of the peripheral blood in these animals certainly suggest sequestration and destruction of the three formed blood elements by the spleen However the authors earlier experiments with splenectomy seem equally clearly to indicate an inhibitory action of the spleen at least on sustained leukocytosis in the rat—Ed]

Splenectomy for Myeloid Metaplasia of Spleen A review of the literature by Thomas W Green C Lockard Conley L L Ashburn and H Raymond Peters[3] (Baltimore) reveals that in 1908 Donhauser suggested that the syndrome of agnogenic myeloid metaplasia is brought about by a primary depression of bone marrow function and that extramedullary blood formation occurs in the liver and spleen as a compensatory reaction There is now widespread belief that removal or irradiation of the spleen destroys an important area of blood formation and that harmful or fatal results will follow This syndrome is generally considered the outstanding contraindication to splenectomy

Vaughan and Harrison (1939) hold that agnogenic myeloid metaplasia is a proliferative disorder of the primitive mesenchymal precursors from which the hemopoietic system takes origin Splenic enlargement may occur when the marrow is cellular and myelofibrosis may develop late

Evidence bearing on the nature of the disorder is provided by observations on the effects of splenectomy Hickling reviewed 27 cases in which operation was done before 1937

(3) New England J Med 48 11 19 Feb 5 1953

Death occurred in 15 in the immediate postoperative period thus reflecting the surgical hazards of that time Patients who survived did not offer impressive evidence of deterioration of the blood picture In a more recent series of 29 cases summarized by the authors consisting of 24 cases from the literature and 5 of their own there were only three deaths in the immediate postoperative period Thirteen patients were alive at the last observation Eight had survived four years There was no evidence that the course of the disease in most splenectomized patients was appreciably different from that in patients not treated with splenectomy The operation did not result in decreased blood formation and was often followed by striking increase in white cell platelet and nucleated red cell counts in the peripheral blood

Although there is little evidence that loss of the spleen per se was harmful no benefit was derived in most cases However in some cases in which hemolytic anemia or thrombocytopenia was prominent splenectomy was beneficial When abnormal bleeding is the result of thrombocytopenia operation is liable to result in elevated platelet counts and improved hemostasis Severe thrombocytopenia seems to be the outstanding indication for splenectomy in patient with myeloid metaplasia The operation is less effective in controlling hemolytic components

It is clear that splenectomy is not indicated in most cases of agnogenic myeloid metaplasia It is equally clear that it does not often lead to failure of the blood forming system

[When the presence of the spleen is suspected to be accelerating red cell destruction it is best to attempt to reduce this by splenectomy The resulting loss of splenic erythropoietic activity although it may appear to be assisting a largely fibrotic bone marrow will usually be of less consequence than the lessened red cell destruction so achieved —Ed]

PURPURAS

Vascular Factors in Pathogenesis of Hemorrhagic Syndromes are reviewed by Theodore H Spaet[4] (Joseph H Pratt and New England Center Hosp Boston) The two major manifestations of the hemorrhagic diseases impaired hemostasis and purpura appear to have separate though related pathogeneses Platelets seem to represent the keystone in the

(4) Blood 7 641 65 J 195

hemostatic arch their agglutination and adhesion to a vascular rent causing the primary arrest of bleeding Permanence and reinforcement are supplied by the fibrin clot which is dependent on blood coagulation factors Vasoconstriction is probably of secondary importance The failure of hemostasis in hemorrhagic diseases is directly related to disorders of platelets and coagulation factors the vessels playing a minor role Purpura and spontaneous hemorrhage however probably stem from vascular disturbances In acute situations the platelets can be maximally depressed or the blood rendered incoagulable without appearance of purpura until the addition of a vascular component The nature of this vascular defect is uncertain Peck Rosenthal and Erf consider petechiae to be dilated capillaries as does Klemperer Orbison has demonstrated capillary and arteriolar aneurysms in thrombotic thrombocytopenic purpura Humble s studies of capillaries in states of increased fragility indicate that petechiae represent extravasations of blood Aneurysm formation as a stage in the development of hemorrhagic lesions is suggested by the work of Krogh

The presence of vascular damage in hemorrhagic diseases with purpura seems certain Bleeding manifestations correlate poorly with the levels of platelets and coagulation factors For example in thrombocytopenic purpuras bleeding after splenectomy may cease before change in the platelet count acute dicumarol® induced incoagulability occurs without bleed manifestations and patients with congenital afibrinogenemia and hemophiliacs rarely display hemorrhagic manifestations unless injured On the other hand purely vascular disorders may result in spontaneous purpura in the presence of normal coagulability as in senile purpura Henoch Schonlein purpura and pseudohemophilia

Roskam reported that a platelet extract was able to increase vascular resistance in experimental purpura without altering the platelet count A splenic extract called splenin by Ungar is capable of shortening the bleeding time increasing vascular resistance and inhibiting the liberation of histamine from injured cells Thrombocytosin a compound of similar properties probably steroid in nature was described by Moolten It was said to increase platelet adhesiveness and to produce partial temporary remissions in thrombocytopenic

purpura without affecting platelet levels Corticotrophin and cortisone may reduce bleeding manifestations and decrease vascular fragility before increase of or without effect on blood platelet levels Ascorbic acid reduces hemorrhagic effects of dicumarol® at given prothrombin levels Thus the therapeutic effect of certain agents in the hemorrhagic diseases appears to depend on their ability to reinforce the vessels and re establish their integrity supporting the concept that vascular damage is mainly responsible for purpura

Although purpura appears to depend on vascular damage clinically a profound drop in platelet count or depression of a circulating coagulation factor is most often associated with a hemorrhagic diathesis This suggests a relation between vascular integrity and the integrity of the coagulation mechanism It is possible that in the turn over of platelets and the various coagulation factors some substance is elaborated which contributes to the normal function of vascular endothelium and cement Depletion of the vascular factor would lag behind depletion of a coagulation factor These speculative concepts fit the paradoxical findings in hemostatic disorders such as faulty coagulability without purpura and purpura with normal coagulability They are consistent with the beneficial effects of agents which do not alter coagulation and with the lag in the appearance of purpura after production of a coagulation defect

[Indeed Bigelow has recently reported tudies of a ub tance derived from platelets during blood coagulation whi h cause contract on of arterial segments in vitro In some pat ents with purpura despite high platelet counts th substance has been found to be decreas d —Ed]

Purpura in Infants and Children Its Natural History David H Clement (New Haven Conn) and Louis K Diamond[5] (Harvard Med School) discuss 140 cases of purpura observed during 1936-47 In all onset of the disease was before age 12 and in about half before age 4 All the patients were white There was a tendency for onset to occur during the winter months Among 44 cases of nonthrombopenic purpura 35 were anaphylactoid 1 was infectious and 8 were due to miscellaneous diseases Of 96 cases of thrombopenic purpura 38 were acute 55 were chronic idiopathic 2 were of chemical origin and 1 was due to splenomegaly Although in this series there were twice as many patients with thrombo

(5) A M A Am J D Ch ld 85 259 78 M b 1953

hemostatic arch their agglutination and adhesion to a vascular rent causing the primary arrest of bleeding Permanence and reinforcement are supplied by the fibrin clot which is dependent on blood coagulation factors Vasoconstriction is probably of secondary importance The failure of hemostasis in hemorrhagic diseases is directly related to disorders of platelets and coagulation factors the vessels playing a minor role Purpura and spontaneous hemorrhage however probably stem from vascular disturbances In acute situations the platelets can be maximally depressed or the blood rendered incoagulable without appearance of purpura until the addition of a vascular component The nature of this vascular defect is uncertain Peck Rosenthal and Erf consider petechiae to be dilated capillaries as does Klemperer Orbison has demonstrated capillary and arteriolar aneurysms in thrombotic thrombocytopenic purpura Humble s studies of capillaries in states of increased fragility indicate that petechiae represent extravasations of blood Aneurysm formation as a stage in the development of hemorrhagic lesions is suggested by the work of Krogh

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found in 13 Heart involvement was difficult to interpret Most patients had normal red and white blood cell counts and normal urinalysis results A few had eosinophilia Platelet counts were all low Bleeding time was prolonged The tourniquet test result was positive in 80% Bone marrow findings were usually normal Splenectomy was performed in 23 cases and there was usually no demonstrable pathology in the spleen

There was much variation in the course of the disease Some recovered within six weeks and others continued to have purpura for almost a year Some had mild bruising for 12 15 years Many girls had metrorrhagia and menorrhagia during the menarche The rate of growth and development was not hindered There were four deaths resulting from bleeding into vital organs such as the brain heart or kidney or from superimposed infection Decisions as to when to give transfusions or when to remove the spleen are important and require sound clinical judgment Thrombopenic purpura in infants and children is frequently a relatively acute illness which progresses to spontaneous cure Splenectomy should not be advised at the onset especially if hemorrhage can be controlled Most recover with no residual damage

The high incidence of demonstrable infection in these cases and the increased incidence of frank allergy are compatible with the hypothesis that an appreciable number of cases of both types of purpura may represent a reaction to a bacterial antigen in a hypersensitive patient resulting in damage to the capillaries platelets or megakaryocytes singly or in combination

[Recent studies of thrombocytopenic purpura in many instances support this concept —Ed]

Bone Marrow in Idiopathic Thrombocytopenic Purpura Analysis of 100 Cases with Reference to Prognostic Significance of Eosinophils and Megakaryocytes Investigators have reported that increased bone marrow eosinophilia is a favorable prognostic sign in idiopathic thrombocytopenic purpura treated conservatively or by splenectomy Similarly an increase in the number of immature megakaryocytes is a favorable sign To evaluate critically the importance of marrow eosinophilia and megakaryocytes in diagnosis and prognosis and to assess the clinical quantitation in individual cases Sophie J Presley William R Best and Louis R Limarzi[6]

(6) J L b & Cl M d. 40 503 514 O t be 195

penic purpura as patients with normal platelet levels non thrombopenic purpura is actually the more common type

In the nonthrombopenic purpura group easy bruising was the most prominent symptom In 65% there was a clearcut history of acute infection close to the time of onset of purpura Upper respiratory infections were the most common and the most commonly isolated organism was hemolytic streptococcus In three fourths purpura followed 11 days after onset of the infection In a few cases there was a history of a double infection of the respiratory tract Few had much fever A family history of purpura was found in five patients Family history of allergy was found in 25% and personal history of allergy in 30% Joint symptoms of pain limitation and swelling occurred in 29 patients Only three had splenomegaly Heart involvement is difficult to interpret but three patients had some cardiac murmurs Red blood cell count and urinalysis results were usually normal Bleeding and clotting times and white blood cell count were normal The tourniquet test result was positive in 10%

These patients did well although the course was frequently punctuated by recurrent bouts of purpura sometimes accompanied by joint pain abdominal pain melena or hematuria They recovered without residual damage There were eight patients who had a longer course with exacerbations and remissions and extensive renal involvement They tended to show gross hematuria nitrogen retention and even hypertension Abnormal signs and symptoms persisted in these patients for several months and they did not return to completely normal health for as long as six months All were finally well although two had evidence of mild nephritis These patients obviously suffered from a diffuse vascular disease The relation of this disease to hypersensitivity is obscure

In the thrombopenic purpura group the chief complaint was easy bruising Of the 96 patients 65 had an acute infection usually of the upper respiratory tract associated with onset of purpura The most commonly isolated organism was hemolytic streptococcus Purpura developed within a week following acute infection in more than half A family history of purpura was found in 17 patients A family history of allergy was present in 30% and personal history of allergy in 15 5% Few patients had joint symptoms Splenomegaly was

kowitz and since then 28 similar cases have been described in the American literature Baehr Klemperer and Schifrin re ported four in 1936 Trobaugh Markowitz Davidson and Crowley reported the first male case in 1946 and Singer and his colleagues gave an extensive account of the disease in 1950 Six cases have been reported in England one by Symmers in 1951 one by Symmers and Barrowcliff in 1951 one by Lennox and Dacie in 1951 one by Smith in 1951 and one by Pagel in 1949

Thrombotic thrombocytopenic purpura occurs at all ages and is more common in females The onset is acute with fever delirium pallor lassitude headache or mental change There are three groups of symptoms and signs namely anemic purpuric and cerebral any or all of which may be prominent Anemia is invariable and severe and mild clinical jaundice is noted in many Purpuric manifestations are common Bleeding evidenced by hematuria melena hematemesis uterine bleed ing and hemoptysis is present in nearly all cases Cerebral symptoms of headache restlessness confusion disorientation convulsions aphasia and mild paresis are common Fever is present in most cases and the spleen and liver may be slightly enlarged

With the exception of four cases all have been fatal within eight weeks of onset There is a normocytic normochromic anemia out of proportion to the degree of bleeding and asso ciated with a reticulocytosis of 30% The hemolytic origin of the anemia is indicated by a retention jaundice increased uro bilinogen and raised hemolytic index The white blood cell count is between 10 000 and 20 000 and a leukemoid reaction is observed terminally Platelets are consistently diminished Bleeding time is increased and capillary fragility is abnormal Bone marrow biopsy shows a normoblastic hyperplasia Post mortem examination shows widespread ecchymotic and petechial hemorrhages of most organs Histologically there are diffuse thromboses of the smaller vessels of all or most of the tissues varying degrees of vascular endothelial hyper trophy and proliferation and little evidence of associated par enchymal damage The thrombi occur in the capillaries and precapillary arterioles In some cases the venules are involved

The disease has seldom been diagnosed during life and there has been no report of a histologic diagnosis during life

(Univ of Illinois) analyzed bone marrow smears from 100 patients with idiopathic thrombocytopenic purpura and compared them statistically with a similar series from normal subjects Criteria for diagnosis included a thrombocyte count of less than 100 000/cu mm and absence of such diseases as lupus erythematosus and leukemia on bone marrow examination and during follow up for at least one year

Eosinophil values were computed from a count of 1 000 late stage granulocytes (neutrophils and eosinophils) in the *metamyelocyte and segmented* stages and expressed as a percentage of late stage granulocytes The dividing line between high and low eosinophil counts was taken to be 4 8% Megakaryocytes were expressed semiquantitatively as none seen decreased adequate or increased Differential megakaryocyte counts were based on 100 consecutive megakaryocytes classified as immature mature or degenerated forms

The authors found no significant difference in marrow *eosinophil counts of the normal subjects and the patients* The patients on the average showed increasingly better prognosis with progressively increasing degrees of marrow eosinophilia However no single figure for the relative number of marrow eosinophils is of practical significance for separating cases of favorable vs unfavorable outcome There was a definite tendency toward increased number and relative immaturity of megakaryocytes in idiopathic thrombocytopenic purpura These megakaryocyte trends were not universally observed and their absence or degree of occurrence appeared to have no prognostic significance Bone marrow examination is primarily of value for differentiating secondary thrombocytopenia from the idiopathic form and to confirm the diagnosis No one should attempt to make the diagnosis of thrombocytopenic purpura on the basis of marrow examination alone Careful clinical and peripheral blood studies should always precede a marrow examination

Thrombotic Thrombocytopenic Purpura Frank Rackow Louis Steingold and J H F Wood[7] (St Andrew s Hosp London) review the literature and describe a case of a rapidly progressive febrile disease characterized by thrombocytopenic purpura hemolytic anemia neurologic *manifestations and fatal* termination The first case was described in 1924 by Mosch

(7) Act m d s d n 143 137 149 195

thrombi Meacham feels that the hyaline material represents an intramural degeneration rather than an intraluminal coagulum Focal vascular lesions have been incriminated by some as the primary lesion with secondary platelet thrombi formation

The disease is more common in women than in men and occurs most frequently in the second and third decades

Clinical course is usually acute with sudden onset of fever weakness pallor jaundice and hemorrhagic manifestations Joint pains may be present and unlocalized abdominal pain is common Moderate hepatomegaly and splenomegaly are usual Central nervous system manifestations most important in pointing to the correct clinical diagnosis consist of hemiplegia facial paralysis aphasia convulsions tremors and reflex changes They may be permanent or transient and may form a major or minor part of the syndrome Changes in the state of consciousness of psychotic behavior may be present Cardiac manifestations are rarely described despite the severity of cardiac lesions

Blood study reveals hemolytic anemia and thrombocytopenia A leukemoid reaction with nucleated erythrocytes and immature leukocytes may be present and also spherocytosis Reticulocytosis is frequent Singer after study of the bone marrow concluded that manufacture of platelets is not inhibited Meacham and the authors believe that thrombopenia may be due more to inadequate formation than to disappearance into platelet thrombi

Differential diagnosis includes conditions which may produce hemolytic anemia and thrombocytopenia such as hereditary spherocytosis acquired hemolytic anemia paroxysmal nocturnal hemoglobinuria hypersplenic conditions and idiopathic thrombocytopenic purpura

Prognosis is extremely poor death usually occurring in a few days to months although the course in one case was three years There may be milder forms of the disease which do not conform to the classic picture

Splenectomy occasionally caused remission but all patients eventually died Most patients were moribund at the time of operation Splenectomy probably deserves further consideration when the diagnosis is made early Penicillin and aureomycin are not effective ACTH may be able to induce a transitory remission

although biopsies of the skin lymph nodes and bone marrow may show the thrombosed blood vessels The disease should be differentiated from Werlhof's purpura polyarteritis nodosa generalized lupus erythematosus and glomerulonephritis Etiology and pathogenesis of the disease are unknown and there is no known treatment

[ACTH or cortisone has been temporarily effective in a few such patients as indeed has splenectomy —Ed]

Thrombotic Thrombocytopenic Purpura Benjamin R Gendel Joseph M Young and Alfred P Kraus[8] (Memphis) add 2 cases to the 30 found in the literature One of their patients showed the characteristic clinical picture with the diagnostic triad of hemolytic anemia thrombocytopenic purpura and transient neurologic manifestations Correct ante mortem diagnosis was made The second patient had a complex course characterized by recurrent thrombophlebitis pulmonary infarctions and refractory leg ulcers probably due to stasis As the condition progressed the picture suggested disseminated lupus erythematosus but L E cells were not demonstrable

Etiology is unknown Baehr suggested an allergic basis because of the resemblance of the vascular lesions to those occurring in the Shwartzman phenomenon Urticaria and drug hypersensitivity are common in patients with this disease the authors patients had penicillin hypersensitivity Thrombotic thrombocytopenic purpura may be related to disseminated lupus erythematosus Nonbacterial verrucous endocarditis has been noted in patients with thrombotic thrombocytopenic purpura Beigelman suggested that differing syndromes result depending on the part of the vessel which acted as the shock organ a reaction in the intima resulting in platelet thrombosis a reaction within the vessel wall in periarteritis nodosa and a reaction in the perivascular mesenchyma in lupus erythematosus

The pathognomonic lesion is the so called platelet thrombus which is widely disseminated throughout arterioles and capillaries of practically all body organs Most authorities believe that the hyaline material which occludes the vessels consists of agglutinated platelets The name thrombotic thrombocytopenic purpura was suggested to indicate that the thrombocytopenia was due to loss of platelets in these

(8) Am J Med 13 3 11 July 1952

A specimen of sternal bone marrow was obtained by needle aspiration The myeloid erythroid ratio was 1 2 07 Study of films stained by Wright s method revealed an extremely cellular preparation with normoblastic erythropoiesis and myelopoiesis both of which were shifted to the left Megakaryocytes were adequate in number and showed little evidence of normal platelet production Reticuloendothelial phagocytosis of erythrocytes and pigment granules was noted Paraffin sections made from solid marrow particles removed during needle aspiration and stained with hematoxylin and eosin revealed hyperplastic marrow The blood vessels were conspicuous because of moderate endothelial proliferation and dilated segments with finely granular thrombi occluding the lumens (Fig 57) Fibroblastic proliferation was noted throughout the substance of some of the thrombi Special stains failed to reveal the exact nature of the thrombotic material A diagnosis of thrombotic thrombocytopenic purpura was made

The patient grew progressively worse and died Autopsy revealed petechiae throughout the organs of the body Hyalinized vessel walls and occluding thrombi were found in many organs Final diagnosis was thrombotic thrombocytopenic purpura with multiple thrombi in the heart lungs and other organs petechiae and hemorrhages in the lungs brain and other organs and multiple small infarcts of the heart and brain and bilateral bronchopneumonia

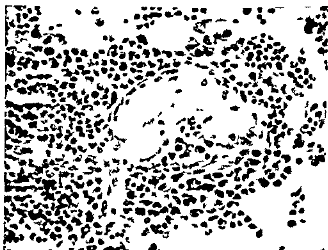
These two cases are the first to be reported in which diagnosis was made histologically before death Aspirated bone marrow is the best material for tissue biopsy although muscle biopsy has been used by some investigators The initial lesion of the small arteries and arterioles is a local hyalin like change in the vessel walls Partial or complete occlusion of the vessels occurs as a result of (1) encroachment on the lumen by protrusion of the mural lesion the endothelial lining remaining intact (2) extrusion of the hyalin like substance from the wall into the lumen (3) propagation of a fibrin or platelet thrombus from the site of endothelial damage or rupture associated with a mural lesion or (4) propagation of thrombus on an extruded mural mass The occluding masses exhibit varying degrees of organization ranging from infiltration by a few proliferating fibroblasts to complete obliteration of the lumen with recanalization of an organized thrombus The cause of the disease is unknown and there is no known treatment

Tuberculosis and Purpura Philip Ellman and J H P Johnson[1] (London) state that the occurrence of purpura in a patient with tuberculosis does not indicate a fatal outcome

(1) B t J T b 46 214 2 Octob 1952

Thrombotic Thrombocytopenic Purpura Confirmation of Clinical Diagnosis by Bone Marrow Aspiration Talbert Cooper J M Stickney Gertrude L Pease and Warren A Bennett[9] (Mayo Clinic) present two cases in which clinical diagnosis was verified before death by demonstration of typical vascular lesions in microscopic sections of sternal bone marrow

Man 48 had not felt well for two months and for three weeks



Fg 57—S t f b w H m t yl d c d f m ×365
(C t y f C p T t l Am J M d 13 374 383 S pt mb 195)

seemed pale and bruised easily He was disoriented and confused and appeared jaundiced Numerous petechiae and ecchymoses were scattered over the body and there was left hemiparesis The hemo globin level was 6 6 Gm and the platelet count 30 000 A blood smear showed occasional microspherocytes extensive polychromasia and numerous normoblasts There was a shift to the left of the myeloid elements The reticulocyte level was 31 2% Bleeding time was prolonged and coagulation time normal Prothrombin time (Quick) ranged from 23 to 28 seconds

A provisional diagnosis of idiopathic acquired hemolytic anemia with associated thrombocytopenia was made However the prom inent neurologic aspects attributed to hemorrhagic encephalopathy suggested the possibility of thrombotic thrombocytopenic purpura. Administration of corti one and penicillin increased the platelet count and reduced bleeding time but the mental state ranged from confusion to transient coma

(9) Am J M d 13 374 383 S pt mb 195

whereas platelets in all other samples were well defined and intact

In Case 2 the percentage of agglutinated platelets in the patient s platelet rich plasma after exposure to quinidine was much higher than after exposure to physiologic saline (Table 2) The same procedure was repeated with a similar outcome

TABLE 1—AGGLUTINATION OF PLATELETS IN PLATELET RICH PLASMA OF CASE 1 BY EXPOSURE TO VARIOUS DRUGS FOR ONE HOUR

PLAT RICH P ASM	Ca % AGG U 1 Pl m	PLATE N N rm 1 Pl m
Quinidine	69 0	0 0
Phenobarbital	3 4	2 8
Priodax®	11 4	11 2
Aspirin	1 8	5 0
Demerol®	4 4	3 6
Saline control	2 4	1 6

I pl t l t h pl m d 0 1 f h drug n phy log 1 fi 1 c t t on f h d g pp m t d 10 mg /100

TABLE 2—AGGLUTINATION OF PLATELETS IN PLATELET RICH PLASMA OF CASE 2 BY EXPOSURE TO QUINIDINE FOR ONE HOUR

P H P MA, 1 Cc	S U ON A 0 1 C	% A UTIN TED PLATELETS I PLA MA	
		th H p D y	n sp D y
Case 2	Phy iol saline	1 8	0 0
Normal	Physiol saline	0 6	0 0
Case 2	Quinidine* in physiologic saline	61 0	17 0
Normal	Quinidine* in physiologic saline	5 6	0 0

F l t t f q d pp m t d 10 mg /100

on the 12th hospital day (Fig 58) There was also agglutination of normal platelets by the platelet poor plasma of Case 2 on exposure to quinidine

The essential factor causing agglutination is in the plasma It persisted for at least 12 days after onset of purpura in the plasma of Case 2 but was absent after 39 days It could no longer be demonstrated in Case 1 after six months The factor survived storage at –20 C for at least 40 days in Case 2

The study appears to confirm that quinidine has the platelet agglutination mechanism described by Ackroyd *in studies* of thrombocytopenia due to sedormid® The thrombocytopenia induced by sedormid® and by quinidine is associated with an abnormal plasma factor which causes platelet agglutination in the presence of the specific drug This in turn probably leads to platelet lysis That platelet lysis accompanies or

prognosis depending on the severity and extent of tuberculosis and being no different from that for similar cases without purpura Tuberculosis causes purpura in various ways In some patients allergy to tuberculoprotein is responsible and may cause anaphylactoid or thrombocytopenic purpura in others hypersplenism is present and in a few purpura follows infil tration or depression of the marrow When panhemocytopenia is found marrow involvement is probable usually following a miliary spread from necrotic glands or abdominal viscera In such cases if there is reason to suspect that the spleen is the major seat of disease splenectomy with administration of streptomycin and PAS should be seriously considered

Boy 13 had pleural effusion due to tuberculosis in 1943 After 11 months of sanatorium care the effusion had completely reabsorbed. In 1945 he had *spontaneous* bruises and petechial hemorrhages The platelet count was 50 000/cu mm After severe epistaxis the red cell count was 3 100 000 the platelets were less than 1 500/cu mm and bleeding time was eight minutes He was given tran fu sions but the platelet count remained low The spleen was not palpable Splenectomy was performed one week later the platelet count was 51 000/cu mm and two months later 170 000/cu mm He made an uneventful recovery and the blood picture remained normal He later had supraclavicular tuberculous lymphadenitis from which he recovered

Platelet Agglutination by an Abnormal Plasma Factor in Thrombocytopenic Purpura Associated with Quinidine Inges tion Frederick S Bigelow and Jane F Desforges (Harvard Med School) studied platelet agglutination in plasma derived from two patients in whom thrombocytopenic purpura ap peared after quinidine therapy In both patients quinidine effected agglutination of the patients platelets in their own plasmas and in Case 2 it also caused agglutination of normal platelets in the patient s plasma In Case 1 1 cc of platelet rich plasma was mixed with 0 1 cc of each of the following drugs quinidine phenobarbital priodax* aspirin demerol* and a saline control the percentage of agglutinated platelets was then compared with that of normal plasma (Table 1) With quinidine there were six times as many agglutinated platelets in the patient s platelet rich plasma as in any other sample patient s or control s Staining showed the agglutı nated platelets to be ragged and partially disintegrated

(2) Am J M Sc 4 274 280 S pt mb 195

gingival bleeding and significant buccal purpura On December 24 temperature again rose to 104 F and there was a fresh efflorescence of petechiae She wa then hospitalized The family hi tory was noncontril utory She had had frequent headaches treated with gynergene and geneserine since age 13 From February to May she had been ill with a fever of 100 2 F suggesting infectious mononucleosis at that time leukocytes numbered 8 000 with 22% monocytes sedimentation rate was 83 in the first hour but results of the Paul Bunnel test were negative The temperature returned to normal in June but in September the sedimentation rate was still 21 in the first hour Finally in November menstruation had been extremely prolonged Examination revealed nothing beyond the picture of febrile anemia with purpura there was no adenopathy and the spleen was not palpable Blood studies on Jan 7 1952 showed type A B Rh positive red cells numbered 1 970 000 and white cells 19 600/cu mm with 70 neutrophils and 2 eosinophils 21 lymphocytes 7 monocytes 20 000 platelets (by hematimeter) and 2% reticulocytes Sternal puncture revealed megakaryocytes in normal quantity with no clumping of platelets Bleeding time was 15 minutes clotting time 22 minutes clot retraction none prothrombin level 70% Bilirubin direct was zero and indirect 1 75 mg /1 000 The direct Coombs test was negative Abnormal agglutinins were not found in plasma albumin with tryp inized red cells at 37 C and 18 C Cold agglutinins were 1/2 No hemolysins were found. Serologic studies were made with serum obtained on this day

Despite antibiotic therapy and the comparatively moderate character of the hemorrhagic syndrome the course was downward ACTH and cortisone were ineffective and repeated transfu ions failed to increase red cell count above 2 000 000 She died in a coma on Jan 11 1952 There was no autopsy

When some of the patient s serum was added to citrated plasma rich in platelets obtained from a donor of the same group it caused agglutination and platelet destruction in less than five minutes (in a paraffin coated tube) the same phenomenon was seen when the material was spread on slides The patient s serum also inhibited clot retraction in normal citrated recalcified plasma under various conditions when thrombin was added to the citrated plasma however clot retraction was not inhibited thereby indicating that calcium had to be present to produce the phenomenon

Various hypotheses are discussed all of them assuming that the patient s serum contained one or more abnormal substances capable of acting on all normal platelets including her own Exogenous intoxication was eliminated because careful inquiry failed to disclose any possibility of accidental



Fg 58—Wrght t d m s f pl t l t h pl ma d l t d w th t th ts vol m f a sol t n f q d ne n phys l gic sal F al q d n cen t t pp m t d 10 mg /100 cc enl g d f m × 50 (Cou t y f B g l w F S d D fo ge J F Am J M Sc 4 274 80 Sept mbe 195)

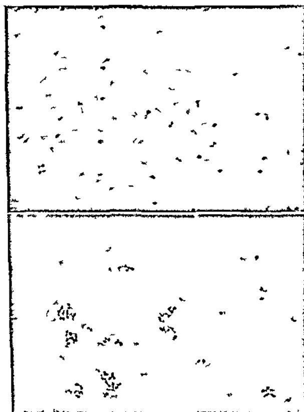
follows quinidine induced platelet agglutination is suggested by the appearance of the platelets in the stained smears in Case 1 and by the in vitro reduction of platelet count in Case 2 Platelet lysis may be the common mechanism of many drug induced thrombocytopenias except those associated with general marrow aplasia and decrease in all formed blood elements

Agglutination and Destruction "in Vitro of Normal Platelets by Serum from Patient with Acute Thrombopenic Purpura Inhibition by Serum of Normal Clot Retraction J Dausset P Delafontaine and Y Fleuriot[3] describe phenomena of massive thrombocyte agglutination and rapid thrombocyte destruction caused by contact between the serum of a patient with acute thrombopenic purpura and normal platelets Such serum was also capable of inhibiting clot retraction in normal blood

Woman 30 had sudden fever and unlocalized malaise on Dec 14 1951 Initial fever 104 F progressively declined in the next few days The first petechiae appeared December 21 followed by

(3) S ng 23 373 384 1952

the bone marrow megakaryocytes with lack of platelet formation an extreme degree of platelet reduction with development of hemorrhagic phenomena and detectable platelet



Fg 59 (top) —Pl t l t l p f t dy f aggl t t g t ty f m d f f m ×400 D k t t ph bj t 1/5 i
Fg 60 (b tt m) —S m fi l] f Fg 59 ft t d t f p t t m d ld ed d f m ×40) D k t t ph bj t 1 5 d
(C y f St f M t l Bl od 8 6 64 J y 1953)

agglutinin in the recipient s serum persisting for 12 14 days The recipient platelets were also found to be coated with a substance capable of reacting with anti human globulin rabbit serum The thrombocytopenia induced in the recipient may be due to a double effect (1) directly on the platelets in the

or deliberate poisoning a list of the drugs taken threw no light on the matter Endogenous intoxication cannot be re jected a priori but blood cultures were negative and anti biotics were given in large doses without effect No allergic process appeared to have been involved since the agglutina tion and destruction of the platelets was produced by the patient s serum without the addition of any other substance The immunologic hypothesis can neither be confirmed nor disproved on the basis of data now available Finally it was impossible to establish the exact cause of the patient s death

[The severe anemia not apparently the result of bleeding indicates that the patient had more than thrombopenic purpura —Ed]

Studies on Platelets IX Observations on Properties and Mechanism of Action of Potent Platelet Agglutinin Detected in Serum of Patient with Idiopathic Thrombocytopenic Purpura (Chronic) are presented by Mario Stefanini William Dameshek Jyoti B Chatterjea Edward Adelson and Irma B Mednicoff[4] (Tufts College) The serum exhibited a circulating platelet agglutinin of high titer This could be demonstrated not only through the ability of the agglutinin to clump various platelet preparations at extremely high titers (Figs 59 and 60) but also to interfere with the functional activity of normal platelets (prevent clot retraction) The agglutinin could be absorbed on packed platelets and when eluted from them its agglutinating activity remained intact The patient s plate lets were found to be coated by an agent capable of reacting with anti human globulin rabbit serum Complement played no role in the reaction of agglutinin and platelets Various properties of the agglutinin were established and electro phoretic studies were carried out The agglutinin was found to be in the β globulin area and to represent 9 33% of the entire serum protein All indications pointed to the charac terization of the agglutinin as a platelet iso (and auto) antibody although this could not be definitely proved

Platelets injected into the patient s circulation disappeared promptly and in presplenectomy experiments capillary fra gility and utilization of prothrombin during clotting tempo rarily became normal returning to original values in four hours Bleeding time was not shortened When the patient s plasma was injected into normal recipients the following series of events occurred striking degenerative changes of

(4) Bl od 8 6 64 Jan a y 1953

than that before splenectomy Prothrombin utilization during clotting and capillary fragility slowly returned to normal On the other hand the appearance of the platelets in the peripheral blood and of the bone marrow megakaryocytes remained unmodified and the bleeding time remained prolonged

The response of splenectomized recipients to the patient s plasma was of the same immediate intensity but of much shorter duration than that of normal recipients Since furthermore splenectomy induced a moderate rise in the patient s platelet count but failed to reduce the concentration of the serum platelet agglutinin it is postulated that in this particular case the thrombocytopenia was probably due to the direct injury of circulating platelets and of the bone marrow megakaryocytes by the circulating agglutinin thus resulting not only in increased destruction but in reduced formation and release of platelets Some experimental results in animals also indicate the possibility of removal of sensitized injured platelets by the intact spleen of the normal animal (Fig 61) This was abolished by splenectomy or ligation of the animal s splenic artery

Method for Separating and Concentrating Platelets from Normal Human Blood Extensive studies of the effects of transfusions of platelet rich blood from polycythemic donors given to patients with thrombocytopenic purpura have suggested the desirability of a method for obtaining large numbers of functionally intact platelets from normal blood Allen H Minor and Lee Burnett (Lenox Hill Hosp New York City) report that a plasma suspension of leukocytes and platelets may be obtained from fresh citrated blood by the addition of an agent which accelerates erythrocyte sedimentation (6% dextran solution) This suspension will contain most of the platelets present in the whole blood Furthermore the addition of a surface active agent (2% triton solution) will permit complete resuspension of the platelets after prolonged centrifugation These observations are the basis of a method which recovers about 80% of the total platelet complement of the blood

Twenty five transfusions of platelet concentrates were given to 11 patients who were thrombocytopenic and bleeding when first transfused Nine presented definite clinical evidence of a hemostatic effect lasting one to five days after a single

(5) Blood 7 693 699 July 1952

peripheral circulation and possibly on those on the surface or emerging from megakaryocytes and (2) damage to the megakaryocyte as demonstrated by the lack of granularity or condensation of granules and protoplasmic vacuolation with consequent inhibition of platelet formation

Various procedures including splenectomy administration of cortisone to the patient and recipient and administration of heparin to the recipient failed to modify the thrombocyto-

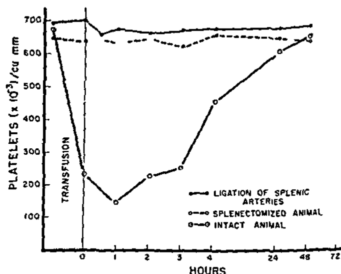
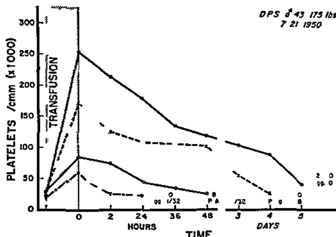


Fig 61 — Effect of intravenous administration of patient's plasma (3 ml/lb body weight) to rabbits normal after splenectomy and after ligation of splenic arteries (Courtesy of Stefanini M et al Blood 8 664 January 1953)

penic response of normal recipients to the patient's plasma although appreciable individual variations in thrombocytopenic response were observed Repeated venesections and replacement with normal blood resulted in a definite reduction in the concentration of platelet agglutinin However the degree of thrombocytopenic response in plasma recipients was not altered although the duration of fall was shortened and was proportional to the agglutinin titer The titer of agglutinin in the patient was unchanged by splenectomy

Splenectomy was followed by a complete arrest of the *bleeding manifestations* and a temporary rise in the platelet count which soon fell to a relatively low level though higher

in the course of the fundamental disea e could be responsible for the acquired state of resistance The refractoriness to platelets may be due to development of isoimmunization against platelets or their products Products of platelet dis integration must possess antigenic properties since devel opment of refractoriness to platelets and of a platelet agglu tinin in a patient receiving blood with few intact thrombo cytes was observed The possibility cannot be excluded that



F g 62—Sh t d l t m f j ct d pl t l t d d l pm t f pl t l t ggl t n n m f p t t w th hypopl t m ec g m lt pl pl t l t t f Sl d d p t t m y t mpl te pl t l t t f on 15 45 m t (C y f St f M et l P S E p B l & M d 80 230 35 J 195)

isoimmunization may have been due to repeated administra tion of incompatible platelets

✓ The cause of decreased platelet survival in patients who had received multiple transfusions but failed to show any platelet agglutinin or platelet destroying agent in their serum remains obscure The negative results may be due to the inadequacy of the technic presently available for detection of antiplatelet agents

✓ [The antigenic properties of platelets apparently render repeated platelet transfusions of diminishing value in thrombocytopenic states Fortunately corticotroph n as well as cortisone have a beneficial effect in

platelet transfusion in the other two patients this effect followed subsequent transfusions Concomitantly there was a return to normal or near normal of bleeding time capillary fragility and prothrombin consumption One pyrogenic reaction occurred Thromboembolic phenomena or other adverse reactions have not been observed

—**Platelets VII Shortened "Platelet Survival Time" and Development of Platelet Agglutinins Following Multiple Platelet Transfusions** Mario Stefanini William Dameshek and Edward Adelson[6] (Tufts College) report on serial determinations of platelet survival time made on four patients two with hypoplastic and two with aplastic anemia All had severe thrombocytopenia and required repeated multiple transfusions of platelet rich polycythemic blood or of isolated platelets for control of bleeding Simultaneously the serum of these 4 patients and of 11 others who had received multiple transfusions of blood over a period of months was studied for platelet agglutinating properties The blood or plasma administered was compatible as to group type and platelets and was given by the direct technic

In three of the four patients the survival time of the injected platelets became progressively shorter and simultaneously the beneficial effect of platelet transfusions on the bleeding manifestations bleeding time capillary fragility and coagulation process became less pronounced (Fig 62) The serum of one patient developed a platelet agglutinin with a titer which rose progressively to 1 32 and remained so until death from cerebral hemorrhage The agglutinin did not seem capable of affecting the functional ability of normal platelets Agglutinins against platelets were not found in the serums of the other two patients who showed increased resistance to transfused platelets

A search for platelet agglutinins in the serum of 11 patients who had received multiple blood transfusions over a period of months showed a low titer platelet agglutinin in one This patient had mild thrombocytopenia and shortened platelet survival time

Results suggest that refractoriness to the therapeutic effects of administered platelets may develop in patients receiving multiple platelet or blood transfusions The pathogenic mechanism involved is difficult to interpret Changes

accompanied by increased platelet production The adminis tration of these hormones interferes with neither spontaneous nor splenectomy induced remission The hematologic changes that occur during ACTH induced remission do not appear to differ from those found during a spontaneous remission The hormones are valuable in (1) tiding patients over an acute episode of thrombocytopenia (2) preparing patients for splenectomy or other surgery (3) treating persistent or

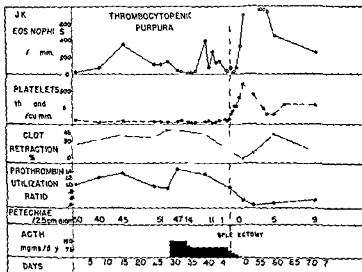


Fig 63 —Id p th th mb ytopen purpura Imp o mert tourn ju t t t d g ACTH th p w thout pl telet m on f ll w d spl ct my Cou t y f F t W W et al Am J M d 13 12 20 J ly 195)

recurrent thrombocytopenia and purpura after splenectomy and (4) in symptomatic treatment of secondary purpura associated with other blood dyscrasias

The hemostatic defect in thrombocytopenia is twofold (1) abnormal vascular fragility which has been consistently responsive to adrenocortical steroid mobilization or adminis tration and (2) reduced production or increased destruction of platelets with concomitant poor clot retraction and prothrombin utilization which are only irregularly corrected by hormonal therapy Platelet production and vascular resistance may be separately influenced by humoral factors

such conditions with or without elevation of the platelet level This is described in the next three articles —Ed]

Hemostatic Defect in Thrombocytopenia as Studied by Use of ACTH and Cortisone William W Faloon Richard W Greene and Eugene L Lozner[7] (State Univ of New York Syracuse) studied four patients with idiopathic thrombocytopenic purpura and three with purpura and thrombocytopenia associated with leukemia during ACTH or cortisone therapy The study was undertaken to establish the relation between adrenocortical function and platelet production and vascular resistance as measured by capillary fragility tests

There was improved capillary resistance under hormonal therapy in the four patients with idiopathic thrombocytopenic purpura Platelet rises which corresponded with improved vascular resistance were noted in only two patients in whom the improved vascular resistance preceded rises in the platelet count In these patients clot retraction and prothrombin utilization ratios improved simultaneously with platelet increases Vascular resistance in all three leukemia patients showed striking improvement but there was no change in the platelet count Of the four patients with idiopathic thrombocytopenic purpura one had a remission after splenectomy after having had only partial remission with ACTH and cortisone therapy another had a remission for at least a year on ACTH therapy the third had a moderate relapse after ACTH and cortisone therapy and the fourth had a splenectomy with sustained remission after 46 days on ACTH (Fig 63) Withdrawal of ACTH in all three leukemia patients was promptly followed by a return of the purpuric manifestations

Splenectomy was carried out during ACTH therapy in two patients with idiopathic thrombocytopenic purpura In one ACTH produced no fall in eosinophils and only a slight fall in the number of petechiae after a tourniquet test The second patient had an indefinite eosinophil response to ACTH but striking improvement in vascular resistance The dosage of ACTH was gradually decreased postoperatively Neither patient bled excessively during surgery and the response to splenectomy was good Neither patient showed evidence of delayed wound healing

The study indicates that these hormones can induce improvement in vascular resistance which is not necessarily

(7) Am J Med 13 12 20 July 1952

Five patients had a remission after medication in three response was continuous in two transitory One patient who had had a recurrence of the disease after splenectomy responded completely to ACTH Cortisone had little effect on the platelet level Another patient who responded to ACTH and later had an excellent postsplenectomy response had a subsequent recurrence of thrombocytopenic purpura (Fig 64) Another patient responded to both ACTH and cortisone two others responded to cortisone none of the three have had a recurrence

Seven patients failed to respond to the hormones five of six who had splenectomy had excellent results

In patients who responded to therapy the interval between the initiation of therapy and the platelet response varied In three response was noted in less than seven days in the other two platelet count did not increase until the 8th and 14th days

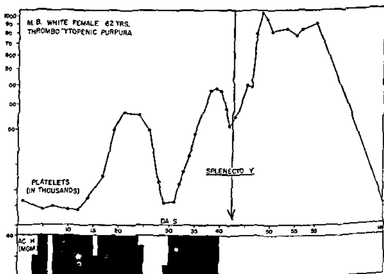
✓The mode of action of ACTH and cortisone in certain patients with idiopathic thrombocytopenic purpura is unknown According to current concepts of the pathogenesis of the disease low platelet levels are believed to result from a suppression of megakaryocytic activity an increase in platelet lysis phagocytosis and the presence of platelet agglutinins and a thrombocytopenic factor in the blood The hormones may affect an unknown immunothrombocytopenic mechanism or may directly affect the spleen and bone marrow There is probably more than one cause for the disease known as idiopathic thrombocytopenic purpura

Use of ACTH and Cortisone in Idiopathic Thrombocytopenic Purpura and Idiopathic Acquired Hemolytic Anemia Muriel C Meyers Stanley Miller James W Linman and Frank H Bethell[9] (Univ of Michigan) state that thrombocytopenic purpura has a number of clinical forms which vary widely in severity but all forms have thrombocytopenia increased capillary fragility prolonged bleeding time and defective clot retraction The bone marrow is active and normal Permanent remissions may occur spontaneously Splenectomy may result in either lasting or temporary remission or may fail to alter the course of the disease Its etiology is unknown but it is believed to result from reticuloendo

(9) A I t. M d 37 352 361 A g t 1952

Possible factors involved in vascular integrity and platelet counts are ascorbic acid immune mechanisms a thrombo cytopenic factor and estrogen levels

Effect of Corticotrophin (ACTH) and Cortisone on Idiopathic Thrombocytopenic Purpura Sloan J Wilson and Gustave Eisemann[8] *(Univ of Kansas) administered ACTH* and cortisone to 12 patients with idiopathic thrombocytopenic



F g 64 —1 t t pond d mm d at ly to ACTH An b t n f ll d *w thd aw l Th w p se to w d ACTH tl py d ple t my wa* d Imm d at p t pe t ve p w ell t b t e b ti f th d se ccu d l t (C t y of W l S J d E m n G Am J M d 13 1 6 J ly 195)

purpura Diagnosis was based on spontaneous purpura decrease in platelets to less than 100 000/cu mm normal clotting and prothrombin times anemia and leukocyto is proportional to bleeding absence of pathologic cells in the blood or *bone marrow* exclusion of history or drugs that are known to cause purpura and absence of an enlarged spleen or enlarged lymph nodes Dosage of cortisone was 50 100 mg daily for at least 14 days if a platelet response was obtained the quantity was gradually decreased then discontinued ACTH dosage was *40 mg daily intramuscularly (or 10 mg* the equivalent intravenously in an eight hour period daily)

(8) *Am J Med* 13 21 26 J ly 1952

purpura were aged 9 72 and the 2 males and 5 females with anemia were aged 16-72

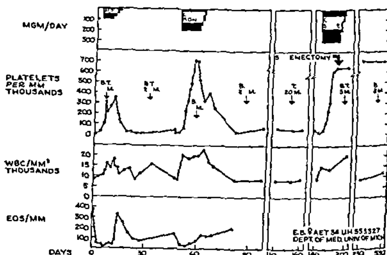
In 12 patients with purpura response to ACTH or cortisone was excellent Platelet counts and bleeding times returned to normal and clinical symptoms disappeared In five the remissions have been sustained for 16-22 months Seven patients relapsed after the cessation of therapy One of these had previously failed to respond to splenectomy in each of the other six a second or third remission was induced successfully and while the hemorrhagic diathesis was under control splenectomy was performed without incident Four patients had incomplete remissions A total of 11 patients had splenectomy There have been no postoperative relapses A single patient who had had a poor response to both ACTH and cortisone had an excellent result from splenectomy The course of a typical patient is seen in Figure 65

In six patients with acquired hemolytic anemia complete control of the hemolytic process was obtained with either ACTH or cortisone When treatment was discontinued the remission was sustained for 15 months in one patient one had a partial relapse and four relapsed to the extent of requiring retreatment in preparation for splenectomy In one patient the cortisone therapy was lifesaving but did not produce a complete remission before surgery This patient failed to attain normal values after splenectomy until cortisone was reinstituted Splenectomy was required in five patients

In neither the purpura nor the hemolytic anemia patients could therapeutic failures be correlated with low dosage schedules or short treatment periods The most satisfactory results were seen in patients who responded to moderate amounts of the hormones after relatively short periods Dosage for those in the purpura group having a good response was 100 mg/day ACTH or 200 300 mg/day cortisone for 8 15 days with maximal response in 3 11 days The dosage for those in the purpura group having fair to poor response was 100 160 mg/day ACTH or 300-400 mg/day cortisone for 11 23 days with maximal response in 6-16 days The dosage of ACTH in the anemia group was 100-160 mg/day for 11 36 days with 6-26 days required to attain a normal hemoglobin level The dosage of cortisone in the anemia

thelial dysfunction especially within the spleen The spleen has been incriminated alternatively as the site of excessive sequestration and increased destruction of platelets and as the source of a humoral agent which inhibits maturation and release of platelets from the marrow or increases their destruction in the circulating blood

Acquired hemolytic anemia is of unknown etiology variable in severity and subject to spontaneous remissions Criteria



F g 65 – Id p th th mb yt p pu pu a t t d w th ACTH cort one and sple t my (C rt sy f Mey r M C *et al* Ann Int Med 37 35 Jul A gu t 195)

for diagnosis include reticulocytosis increased bile pigment metabolism and evidence of autoimmunization Splenectomy may be curative Demonstration of a thrombocyte agglutinating factor in the serum of patients with thrombocytopenic purpura suggests a common etiology for the two disorders Since the spleen is a lymphoreticular organ knowledge that the administration of ACTH or cortisone modifie lymphoid and reticuloendothelial activity provides a rational basis for the use of these agents in these two diseases

Over 22 months 17 patients with thrombocytopenic purpura and 7 with acquired hemolytic anemia were treated with ACTH or cortisone or both The 5 males and 12 females with

60 Estrogen therapy was undertaken because of the appar ent relation between recurrent epistaxes and the menstrual cycle in one patient She had nasal hemorrhages one to five days before the end of secretory phase but they disappeared shortly after onset of the menstrual period Because the epi sodes of epistaxis bore a striking relation to the periods of decreased estrogen excretion and increased urinary gonado trophin excretion it was theorized that estrogen replacement therapy might be of benefit A dose of 0 5 mg ethinyl estradiol was given twice daily One week after therapy was started the mucous membrane had returned to a normal pink glisten ing texture By the third week the epistaxes had disappeared During the fourth week estrogen therapy was discontinued because of sodium retention and edema Epistaxes returned when estrogen was withdrawn A daily dose of 0 25 mg was found adequate to restore the nasal mucous membrane to normal and control epistaxis without producing sodium re tention

The men responded to a dose of 0 5 mg ethinyl estradiol and 5 mg methyltestosterone daily the latter being given to counteract the feminizing side effects of ethinyl estradiol

In all patients the nasal mucosa returned to normal one to three weeks after treatment was initiated and the epistaxes decreased in number and severity concomitant with the mucous membrane changes The mechanisms by which estro gen therapy produced these effects are unknown

[This clearly deserves further therapeutic trial in a cond tion notori ously difficult to control —Ed]

COAGULATION DEFECTS

Reading of the articles in this chapter ind cates the present and in creasing degree of complexity of this field The exact recogn tion of many of these disorders requires precise technics performed with a precision that can be gained only with experience Fo tunately aside from hemo philia and prothrombin deficiency most are rare The poss bility that operative procedures may cause fibrinolysis or that obstetric conditions may result in rapid defibrinat on with or without fibrinolysis should be borne in m nd T ansfusion of fresh blood and with fib inogenopenia the intravenous injection of prepared fibrinogen remain the most generally useful therapeutic proced res —Ed

Mild Hemophilia An Allelic Form of the Disease John B Graham William W McLendon and K M Brinkhous[2] (Univ of North Carolina) described the disease in a large

(2) Am J M S 2 5 46-53 J ry 1953

group was 300 mg/day for 19 28 days with 12 24 days required to attain a normal hemoglobin level Neither increasing the dose nor extending the treatment period enhanced the therapeutic effect in the purpura group whereas increasing the treatment period did enhance the therapeutic effect in the anemia group

ACTH or cortisone may modify the course of these two diseases by producing changes entirely analogous to those observed in spontaneous remission Although the remissions may not be sustained they are valuable in preparing patients for splenectomy Intensive courses of ACTH and cortisone in the immediate preoperative period do not interfere with wound healing Failure to respond to ACTH and cortisone does not preclude a therapeutic response to splenectomy Patients with incomplete remissions after splenectomy may be benefited by ACTH or cortisone

There is a reciprocal relation between the spleen as a lymphoreticular organ and the adrenal cortex as illustrated when ACTH or cortisone is given to patients with hypersplenic conditions The administration of ACTH and cortisone for hypersplenic disorders may restore hematopoietic equilibrium through a combination of effects including modification of immune body reactions diminished splenic hypersequestration and hyperphagocytosis and myeloid stimulation

Hormonal Management of Hereditary Hemorrhagic Telangiectasia Henry J Koch Jr George C Escher and John S Lewis[1] (Memorial Cancer Center New York City) report a decrease in the incidence and severity of epistaxes due to telangiectasia of the nasal mucous membrane in five patients who received estrogen or combined estrogen and androgen therapy The condition is hereditary manifesting itself in localized dilatations of the capillaries and venules which form distinct groups of telangiectasias These occur on the skin of the face and nasal and buccal mucous membranes and give rise to profuse hemorrhage either spontaneously or as a result of trauma No evidence of a blood dyscrasia exists except that associated with chronic blood loss The commonest symptom is epistaxis but other mucous membranes or the skin may be the exclusive sites of hemorrhage

The patients three women and two men were aged 42

(1) J.A.M.A 149 1376-1380 A g 9 195

(Owren) and the factor of Fantl and Nance It is present in fresh normal whole blood or plasma and is unequivocally distinct from serum prothrombin conversion accelerator (SPCA) and its precursor deficiency of which results in another form of pseudohypoprothrombinemia

Characteristics of the disease include normal platelet count increased bleeding and clotting times and normal clot retraction The prothrombin time of the whole plasma as well as that obtained by the dilution technic is prolonged The two stage prothrombin conversion is negligible unless a nonprothrombin factor AC globulin is supplemented The labile factor activity is less than 5% of normal The plasma is devoid of AC globulin activity and there is no factor V activity Purified prothrombin derived from the pathologic plasma is normal and the plasma antithrombin activity is normal The prothrombin consumption during spontaneous coagulation is retarded but the prothrombin completely disappears if sufficient time is allotted Platelet agglutination is retarded The plasma defect in this disease is similar to that in aged normal plasma In parahemophilia SPCA formation from its precursor in plasma is normal despite the retarded prothrombin consumption and negligible AC globulin concentration Normal AC globulin activity is not required for SPCA formation

The defects of parahemophilic plasma can be rectified by fresh whole blood and plasma dicumarol® plasma phenyl indanedione plasma and SPCA deficient plasma but not by vitamin K With blood transfusions the prothrombin time is restored toward normal the prothrombin conversion and prothrombin consumption improve and the bleeding and clotting times are restored toward normal Elective surgery was performed safely in one patient when blood transfusions were used The blood must be fresh because AC globulin deteriorates fairly rapidly under ordinary conditions of storage

The hypoprothrombinemias should be reclassified as true hypoprothrombinemia and pseudohypoprothrombinemia True hypoprothrombinemia may be congenital or acquired The acquired form may be idiopathic due to liver disease vitamin K deficiency or drug induced Pseudohypoprothrombinemia may be due to AC globulin deficiency which may be congenital or secondary to liver disease or purpura fulminans or to SPCA deficiency which may be congenital or due to dicumarol® poisoning

family 79 living members including 14 affected men and boys studied through four generations There was no history of hemarthrosis or fatal hemorrhage Results of the usual clotting tests including prothrombin consumption were normal or equivocal Diagnosis depended on demonstration of definitely reduced antihemophilic factor (AHF) in the plasma

The clotting defect in the men is probably borderline and allows them to sustain slight injury with little or no difficulty However with more extensive injury e g tooth extraction the available supply of AHF may be seriously depleted and prolonged bleeding may result There is no clear history of hemorrhagic tendency in the women

The disease like classic hemophilia seems to be transmitted as a sex linked recessive characteristic Some of the heterozygotes show a diminution in their plasma AHF Bleeder men with one exception had an AHF level of 20-25% normal controls 68 149% About half the heterozygous women had AHF concentrations between these two ranges It should be possible to detect the heterozygous state in these women before childbearing The foregoing implies that the gene is not completely recessive It may be an incomplete recessive carried on the X chromosome

The differences between classic hemophilia and this mild disease led the authors to postulate the existence of an allelic mutant responsible for the mild disease It is proposed that this allele of the normal dominant gene H and the classical hemophilia allele h be designated h^m It is possible that there are other alleles dominant and recessive which are part of this series of multiple allelomorphs

Parahemophilia in Three Siblings (Owren s Disease) Studies on Certain Plasma Components Affecting Prothrombin Conversion Benjamin Alexander and Robert Goldstein[3] (Harvard Med School) studied three siblings with parahemophilia only one of whom had hemorrhagic phenomena The disease probably congenital is a form of pseudohypoprothrombinemia and is due to deficiency of a nonprothrombin plasma constituent which is essential for the rapid physiologic conversion of prothrombin to thrombin by thromboplastin and calcium This substance called AC globulin is identical with labile factor (Quick) factor V or proaccelerin

(3) Am J M d 13 255 72 S ptemb 195

index of the therapeutic effect of transfusion. As much as 4 pt of whole blood may be required to control hemorrhage in an adult.

Hemophilia with Two Circulating Anticoagulants: Clinical and Experimental Study is reported by H. G. Kupfer, R. Thagard, H. Irvin, D. Lipford and J. B. Parker[5] (Med. College of Virginia). Lack of antihemophilic globulin per se is not sufficient explanation of bleeding episodes in hemophilia. Fluctuation of some other agents such as circulating anticoagulants may be responsible for the fact that at one time a certain trauma will cause bleeding and at another will not.

Negro boy, 11, was first hospitalized in August 1949 with a hematoma of the right thigh and hemarthrosis of the right knee with contracture and ankylosis. Family history was normal. He had had a bleeding tendency since infancy. At age 7 he had received his first blood transfusion—for recurrent epistaxis and joint and muscle swelling following trauma. He had normochromic normocytic anemia, slight leukocytosis and prolonged clotting time. Capillary fragility could not be evaluated because of the dark pigmentation. Hemophilia was diagnosed and he was treated with two 500 cc transfusions and multiple correction casts on the right knee. In February 1950 on second admission anemia and prolonged clotting time were treated with 600 cc whole blood. During third admission (October 1950 to January 1951) a heparin level of 12 gammas % was consistently found. Clot retraction, which had been normal, became prolonged. Studies also revealed the presence of antihemophilic globulin antibodies. A total of 210 mg protamine sulfate given intravenously in five days reduced heparin levels to zero and stopped bleeding. He also received 400 cc whole blood and 200 cc plasma. On hospitalizations two and four months later the heparin level was still zero.

Platelet levels and clumpiness, bleeding time and the one stage prothrombin times were normal. Changes in fibrinogen level were not significant. Abnormal clotting time ranged from 70 to 250 minutes. Antihemophilic globulin added to the patient's blood brought clotting time to normal. Before treatment with protamine sulfate the patient's blood contained two circulating anticoagulants and recalcification time of oxalated plasma was 105-480 seconds. After therapy recalcification time was 130 seconds, then stabilized at 180-192 seconds, suggesting that an anticoagulant of the antibody type has little effect on recalcification time. After neutralization of the heparin the patient's plasma was still able to prevent clotting in normal blood. Antithromboplastic or increased antithrombin activity could not be demonstrated. The patient's plasma contained significant quantities of antibodies to antihemophilic globulin when tested

(5) Virginia M. Month. 79:6 9-639, November 195

Christmas Disease A Condition Previously Mistaken for Hemophilia is described by Rosemary Biggs A S Douglas R G Macfarlane J V Dacie W R Pitney C Merskey and J R O Brien[4] (Plymouth England) They found seven patients with a clotting defect which clinically and by ordinary tests would be classed as hemophilia However blood or plasma from these patients corrects the clotting defect of hemophilic blood and vice versa The prime defect in this new disease named after the first patient studied is a delay in blood thromboplastin formation due to absence or deficiency of a plasma factor—not antihemophilic globulin—which is called the Christmas factor This substance is in the crude alpha and beta globulin fractions of normal plasma and is precipitated at between 33 and 50% saturation with ammonium sulfate It is present in normal and hemophilic serum is destroyed by heating plasma to 56 C for 10 minutes and is removed by Seitz filtration It is stable on storage is adsorbed by $Al(OH)_3$ and a substance closely resembling it is reduced in patients treated with ethyl biscoumacetate

Christmas disease has an apparently sex linked recessive inheritance but the defect may not be completely recessive Bleeding time capillary fragility platelet count and prothrombin time are normal Whole blood clotting time and prothrombin consumption are abnormal Preliminary differentiation from hemophilia can be made by studying the in vitro effect of normal and hemophilic plasma on the calcium-clotting time of the patient s plasma An exact distinction can be made by using a thromboplastin generation test which permits control of the presence or absence of either antihemophilic globulin or Christmas factor in the reaction mixture

Among cases usually classed as hemophilia there are two distinct entities Most hemophilic patients lack antihemophilic globulin some lack a serum factor (Christmas factor) related to but different from factor VII of Koller Differentiation is important as treatment for the two conditions is different In Christmas disease potent antihemophilic globulin preparations do not correct the clotting defect in vivo or vitro It also seems that stored blood or plasma is more effective than fresh blood in controlling bleeding The thromboplastin generation test may be the most sensitive

(4) Brit M J 2 1378 138 Dec 27 1952

nomenon was positive Serum protein concentration was 8 47% and viscosity 3 4 Acid phosphatase level was 0 55 units and alkaline phosphatase calcium and phosphorus values were normal The formol gel reaction was positive Urea content was 49 mg /100 ml Bleeding coagulation and prothrombin times were normal cloud ing on heating to 40 C no dissolving on further heating to 100 C A lymph node smear showed numerous lymphoid cells with little protoplasm 1 2 nucleoli and ome mitosis Electrophoresis showed 53 1% zeta globulins and ultracentrifugation revealed macroglobu lins Rabbit antimacroglobulin serum causes precipitation in a 1 2 000 dilution Lymph node biopsy showed lymphoid reticulosar coma

Treatment with antibiotics hemostyptics transfusions vitamins diamidin and cortisone was unsuccessful He died of intestinal bleed ing five months after hospitalization Autopsy revealed numerous typical and atypical plasma cells and pla macellular reticulum cells in addition to lymphoid forms in bone marrow lymph nodes liver and spleen Histologic diagnosis was lymphoid reticulo arcoma with transition to diffuse myeloma

No lymphadenopathy or hepatosplenomegaly was found in another patient The peripheral blood sometimes showed an increase of lymphocytes and some plasma cells The bone mar row picture was one of abundant lymphoid cell forms

Waldenstrom s macroglobulinemia presents a fairly uni form morphologic picture sometimes predominantly plasma cellular sometimes lymphoid reticulocellular In this case there was a change from lymphoid cellular reticulum sar coma to diffuse myeloma

All three patients in this study revealed macroglobulin emia in two instances zeta hyperglobulinemia and in one gamma hyperglobulinemia Molecular weight for the zeta fractions was 200 000 Zeta globulins not found in normal serum seem to indicate a severe disturbance of the serum proteins

Definite diagnosis can be established not only by demon strating macroglobulins but immunologically by means of rabbit antiserum developed against macroglobulins

Macroglobulinemia must be distinguished from primary hyperproteinemia e g after viral infections premyelotic con ditions and atypical lymphatic leukosis Waldenstrom s mac roglobulinemia is classified as a reticulosis and often the primary diagnosis is reticulosarcoma The important thing is not the sarcomatous change specifically but rather a neo plasia of the reticulohistiocytic system In rare cases only

in a precipitation test using antihemophilic globulin as the antigen

This is the ninth such case reported The authors suggest that blood transfusions may initiate a vicious cycle by stimulating production of antibodies to antihemophilic globulin if this is true plasma should be used only when other hemostatic methods fail They feel that hemophiliacs should be followed by studies of antihemophilic globulin levels and antibody levels to learn whether bleeding correlates with a fall in one and a rise in the other It is suggested that hyperheparinemia may be a reticuloendothelial dysfunction

Clinical Picture and Differential Diagnosis of Waldenstrom's Macroglobulinemia The disease begins with prolonged weakness paleness shortness of breath oral and nasal bleeding more or less generalized lymphadenopathy and rarely also splenohepatomegaly Histologically the lymph node structure is destroyed and aggregations of lymphocytoid small cells with fine chromatin pattern and nucleoli are noted Depending on the stage of the disease normochromic anemia and a normal or slightly increased number of leukocytes with increasing lymphocytosis can be seen Platelet count and bleeding and coagulation times are normal Sedimentation rate usually exceeds 100 mm /hour The gel reaction of plasma is fast with spontaneous gelification after cooling Serum viscosity is exceptionally high There is sometimes a Bence Jones like proteinuria with protein precipitation at 45 C but no dissolving on further heating Final diagnosis depends on demonstration by ultracentrifugation of giant protein molecules with a molecular weight to 1 000 000

Other authors have indicated that peripheral circulatory disturbances (acrocyanosis and Raynaud s disease) due to gelification of the serum are rather common F Schaub[6] (Aarau Switzerland) discusses differential diagnosis and reports on three cases

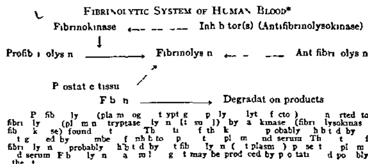
Man 70 had axillary inguinal and cervical lymphadenopathy and chronic bronchitis On hospitalization cachexia generalized lymphadenopathy and bronchitis were noted The liver was 2 finger breadths down and the spleen was palpable Skeletal x rays showed slight generalized osteoporosis Sedimentation rate was 102 mm / hour hemoglobin concentration 63% erythrocytes numbered 3 080 000 and color index was 1 05 Leukocytes numbered 8 400 with 70% neutrophils 7 5% monocytes 17 5% lymphocytes and 5% plasma cells Platelets numbered 410 000 Rumpel Leede phe

(6) S hw z m d Wch h 82 890 895 S pt 6 195

was still depressed and in the dangerous range Average level 24 hours after injection was 53 5% Results in the two patients given synthetic vitamin K resembled those in the controls

↓ The following two articles discus the development of hemorrhagic conditions due to sudden reduction of fibrin or fibrinogen in certain pathologic conditions —Ed

Fibrinolysis and Fibrinolytic Purpura Mario Stefanini[8] discusses the increased interest in the series of events which have led to the recanalization of the blood vessels after hemostasis has been achieved Fibrinolysin by its ability to digest the fibrin clot plays a significant part in this process Fibrinolysin is present in the circulating blood as an inert proenzyme which may be activated The degree of activation



depends on the delicate equilibrium between activators and inhibitors

Fibrinolysin is important in the pathogenesis of some hemorrhagic diatheses The activation of profibrinolysin to fibrinolysin is brou ht about by kinases which are found in many tissues Tissue damage such as surgical trauma burns hemorrhage shock transfusion reactions disseminated carcinoma and severe parenchymal liver disease may activate the fibrinolysin Severe hemorrhagic disturbances may be associated with metastatic carcinoma of the prostate Prostatic fibrinolysin may enter the circulation when produced by widespread neoplastic prostatic tissue This fibrinolytic agent similar to but not identical with plasma fibrinolysis can be isolated from normal prostatic tissue A severe hemorrhagic

(8) Blood 7 1044 1046 O be 195

proliferation of this system is seen in connection with macro globulinemia in other cases it may be impossible to distinguish it morphologically from a myeloma Demonstration of macroglobulinemia will, however always provide the diagnosis

The course of macroglobulinemia is usually more protracted than that of other tumors of the reticulohistiocytic system and usually extends over some years Prognosis is however the same Therapy is exclusively symptomatic

[The analogy between myelomatosis with hyperglobulinemia and Bence Jones proteinuria appears to be close —Ed]

Effect of Intravenous Injection of Emulsified Vitamin K_1 on Hypoprothrombinemia Induced by Tromexan® Tromexan® effectively induces hypoprothrombinemia however severe hemorrhages have followed its use Because vitamin K_1 reverses dicumarol® induced hypoprothrombinemia William C Van Buskirk John S Belko and Thomas J Giovanniello[7] (V A Hosp West Roxbury Mass) studied its effect on 18 patients in whom hypoprothrombinemia was therapeutically induced and maintained by tromexan®

An emulsion of purified naturally occurring fat soluble vitamin K_1 in a dose of 50 mg /kg was administered intravenously to 10 patients To avoid a pyrogenic reaction 1 cc was given slowly over 2 minutes and the remainder of the dose over 15 minutes Two patients received single intravenous injections of 75 mg of a synthetic water soluble vitamin K preparation (synkayvite®) All injections were given 16 hours after the last dose of tromexan® The other six patients served as controls and received no antagonist the tromexan® effect being allowed to disappear without interference

Prothrombin activity was demonstrably elevated in all 10 patients who received vitamin K_1 in fat emulsion Within three hours after injection it was twice its original level and outside the dangerous range Average prothrombin level 24 hours after injection was 73 2% Two patients had a relative resistance to subsequent immediate administration of tromexan® Both required about twice the former dose to produce therapeutic hypoprothrombinemia a second time There were no untoward effects

In the six controls prothrombin activity returned gradually to normal Eight hours after injection the prothrombin level

(7) New Engl d J Med 48 57 58 Ja 8 1953

the degree of lysis Complete dissolution indicates afibrinogenemia partial dissolution indicates hypofibrinogenemia [Rather this is a measure of plasma fibrinolytic activity because without fibrinogen no clot would form initially —Ed]

CASE 1 —Woman 21 gravida II had received a transfusion at age 9 The blood type was O Rh negative The husband had type B Rh positive blood The wife s anti Rh agglutinin titer ranged from 1 4 to 1 64 She delivered a fetus that lived and she had no po tpartum difficulti s One year later she was again pregnant and the anti Rh agglutinin titer was 1 256 After 28 weeks approximately 6 weeks after fetal death sudden profu e vaginal bleeding began A few hours later she delivered a macerated fetus and continued to bleed vaginally The clot dissolution test revealed afibrinogenemia She stopped bleeding after receiving 3 500 cc fresh blood The blood continued to show some lysis 36 hours after delivery Recovery thereafter was uneventful

CASE 2 —Woman 28 gravida VI had had one normal pregnancy and four stillborn or erythroblastotic infant After the ec ond pregnancy it was found that her husband had Rh po itive group O blood and was believed heterozygous She had shown some anti Rh agglutinins in her previous pregnancies After the third pregnancy it was learned that her husband s blood was Rh_2 Rh and he was suspected of being homozygous During the sixth pregnancy the fetus died in utero at about five month Fifteen weeks later the mother began to discharge bloody urine bleed vaginally and show ecchymotic areas on the skin After delivery of a macerated fetus she had massive vaginal bleeding and was treated with blood transfusions and vaginal and uterine packings An emergency vaginal hysterectomy was necessary to stop the bleeding She rapidly improved Her blood showed hypofibrinogenemia for a few months then became normal [Ordinarily after delivery as soon as bleeding or shock is controlled fibrinogen values become normal within a few hours —Ed]

CASE 3 —Woman 26 gravida III had had one normal and one erythroblastotic baby During the third pregnancy her blood was grouped A Rh negative with a positive titer of anti Rh agglutinins of 1 64 or possibly 1 128 against the C and D factors of the Rh compl x Her husband was classed group A Rh positive subtype R definitely homozygou and of genotype CDe/CDe The fetus di d after 23 week gestation Two months later there was severe vaginal bleeding after delivery of the extremely macerated fetus The maternal blood showed hypofibrinogenemia She was treated with blood transfusions and 2 Gm fibrinogen The bl eding stopped and she recovered

Fibrinogen therapy may obviate the need for hysterectomy in such cases Adequate preoperative preparation with fibrino gen should be made whenever hysterectomy is necessary

tendency may accompany premature separation of the placenta in which the fundamental defect is pronounced hypofibrinogenemia or even afibrinogenemia This may be an example of activation of fibrinolysin due to the passage of placental tissue into the circulation Such patients are treated by emptying the uterus and administering large amounts of fibrinogen

Fibrinolysin may cause a complete breakdown of the hemostatic mechanism to an extent seldom observed in other hemorrhagic diatheses The severe bleeding which follows fibrinolytic purpura is probably due to enzymatic digestion not only of the fibrin clot but also as indicated by survival studies of these agents in vivo of fibrinogen and in some cases of all other proteins involved in the process of blood coagulation Fibrinolysin should be considered when there is a bleeding disease which cannot be explained by other more obvious causes or when many coagulation factors appear to be involved simultaneously Qualitatively fibrinolysin can be detected by simple laboratory methods [such as watching for lysis of clotted blood samples placed in the incubator —Ed]

Treatment of fibrinolytic purpura is difficult Until the cause for activation or production of fibrinolysin has been removed administration of whole blood plasma and its fractions may be largely ineffective because the coagulation proteins needed to restore the hemostatic process are destroyed at a greatly accelerated rate Removal of the cause often requires extensive surgery Tagnon *et al* have isolated a specific inhibitor of prostatic fibrinolysin effective *in vivo* and in vitro which may be used in some cases Cortisone may reduce the activity of fibrinolysin and stilbestrol may be specific in certain cases of disseminated cancer of the prostate

Rh Isosensitization, Intrauterine Fetal Death and Hypofibrinogenemia Charles H Peckham Jr (Manchester Conn) and Louis F Middlebrook[9] (Hartford Conn) report on three cases of hypofibrinogenemia in Rh isosensitized multigravidas carrying dead fetuses A simple clot dissolution test will establish the absence or diminution of the fibrinogen content of the blood To determine this 5 cc venous blood is incubated at 37 C and the clot is periodically inspected for one hour for

(9) Am J Ob t & Gyn 65 644 650 M ch 1953

developed with death of the fetus in utero Four days later because of signs of early labor a macerated fetus was delivered by cesarean section This also disclosed three retroplacental clots the largest of which occupied more than half of its surface The postoperative course was smooth. She was discharged after 11 days but died suddenly 3 days later Pathologic examination showed widespread venous thromboses and infarction of multiple organ systems Histologically there were multiple diffu e thrombi many composed predominantly of fibrin (Fig 66)

Fibrin embolism a pathologic process occurring in human pregnancy may well be responsible for some of the later complications which have been described as hemorrhagic diathesis of pregnancy obstetric shock cardiac failure and pulmonary edema This process most often occurs during the last trimester and is seen especially in premature separation of the placenta It has been shown that the human decidua and placenta are rich in thromboplastin In certain abnormalities of human pregnancy mostly abruptio placentae excessive amounts of thromboplastin are forced into the peripheral circulation and the formation of fibrin from fibrinogen is initiated This produces the so called fibrin embolism a disseminated deposition of fibrin which may if extensive cause occlusion of the circulation These occlusions are most often microscopic and must not be confused with the ordinary types of emboli or thrombi In the extreme however fibrin deposition may be extensive enough to occlude vital organs and cause death

Paradoxically however should the patient survive fibrin formation all circulating fibrinogen may have been consumed with resultant fibrinopenia and consequent failure of the clotting mechanism The patient is then in jeopardy of hemorrhage especially at parturition

Simple termination of pregnancy is no guarantee for cessation of the pathologic process Decidua retained at the retroplacental site may continue to release thromboplastin into the circulation during uterine involution Diagnostic methods must be developed and criteria defined whereby decisions concerning the extent of intervention (hysterectomy) may be determined in future instances

[Weiner and Reid believe that a dead fetus even without placental separation may be the source of thromboplast c material when labor begins The defibrination" of the patient commonly leads to hemorrhage with or without shock and fibrinolysis In such patients the use of concentrated preparations of fibrinogen intravenously may be life saving —Ed.]

Intravascular Clotting Complications of Pregnancy, observed in two patients are discussed by Lennard L Weber David R Meranze and Frank Kaplan[1] (Mount Sinai Hosp Philadelphia) The first a patient with abruptio placentae developed intractable bleeding and died from this cause following hysterectomy despite 13 transfusions The second is described here

Woman 24 gravida III had a normal pregnancy except for



F g 66—F b n th mb n ap lla f l g × 330 (Co t y f W be L L t al Am J Ob t & Gy 64 1037 1048 N embe 1952)

hypotension until the beginning of the sixth month when cerebral thrombosis with right sided hemiplegia developed At this time prothrombin time (modified Quick one stage) recalcified clotting time in glass and silicone bleeding time protamine titration and antithrombin time were normal Lee White clotting time was slightly accelerated The patient s deprothrombinized plasma shortened the prothrombin time of whole normal plasma This effect disappeared in five days Six weeks later acute thrombosis of a vessel of the right leg developed without evidence of infection At the end of the seventh month sudden hypertension and albuminuria

(1) Am. J Ob t. & Gynec. 64 1037 1048 No mb 1952

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON M D

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL AND RHEUMATIC HEART DISEASE

Diagnosis and Management of Common Malformations of the Heart are discussed by Helen B Taussig[1] (Johns Hopkins Univ) Diagnosis of patent ductus arteriosus is generally based on the presence of a continuous murmur over the pulmonary area without signs of cyanosis X rays commonly show fulness of the pulmonary conus and slight left auricular enlargement With cyanosis or polycythemia surgical closure of the ductus is almost inevitably contraindicated As continuous murmur seldom develops before age 4 diagnosis before then is often difficult but fortunately also is usually not necessary as the defect causes little or no disability A large patent ductus may sometimes cause great cardiac enlargement in early infancy Such patients if murmurs are only systolic or both systolic and mid diastolic but not continuous should be referred to a specialist Patent ductus when it is an isolated malformation is treated by ligation with or without division

Coarctation of the aorta is diagnosed on the basis of a strong pulse in the upper and a weak or absent pulse in the lower extremities Often there are pulsating vessels and sometimes a systolic murmur in the interscapular area Notching of the ribs usually not apparent until puberty is the most characteristic sign Surgery is indicated for severe hypertension or left ventricular strain

A vascular ring encircling the trachea and esophagus may be diagnosed on the basis of stridor and dysphagia and roentgen evidence of constriction of the trachea or esophagus Surgical division of the smaller component of the ring is curative if done before constriction becomes permanent

(1) C cul tion 6 930 940 D cembe 1952

cyanosis the fainter the murmur Such children often have to squat during exercise Surgery is most successful between ages 8 and 14 and results are good

Tricuspid atresia closely resembles the tetralogy of Fallot except that the ECG shows left ventricular hypertrophy and left axis deviation When it is associated with pulmonary stenosis management and treatment are the same as for the tetralogy of Fallot although operative mortality is nearly twice as high

In pure pulmonary stenosis (pulmonary valvular stenosis with an intact ventricular septum) the heart is greatly en larged if the stenosis is severe and the pulmonary artery dis tal to the stenosis is dilated There is generally a harsh sys tolic pulmonary murmur and a weak pulmonic second sound The ECG shows severe right axis deviation and right ven tricular hypertrophy or right bundle branch block If the foramen ovale is completely sealed there is no cyanosis Ex ertion increases dyspnea If the heart size is normal there may be no symptoms Cardiac enlargement precedes symptoms Valvulotomy is indicated if the right ventricle is significantly strained Cyanosis is also an indication for operation

In the Eisenmenger complex pulmonary blood flow is greatly increased and there are pulmonary and right ventricu lar hypertrophy There is usually a systolic murmur and x ray evidence of a full pulmonary conus prominent pulmonary artery and a hilar dance It is as yet not operable

The Taussig Bing malformation (transposed aorta com bined with over riding pulmonary artery) causes cyanosis from birth generally with little paroxysmal dyspnea The slightly enlarged heart has a soft systolic murmur and the second pulmonic sound is accentuated and often reduplicated X ray reveals fulness of the pulmonary conus and increased hilar shadows with expansile pulsations It differs from the Eisenmenger complex in that the cyanosis dates from birth Creation of an auricular septal defect may be beneficial

Complete transposition of the great vessels often causes early death Usual signs are a systolic murmur and a gallop rhythm There are engorgement of the liver and congestion in the lungs X ray reveals that the heart is enlarged to both right and left and the ECG shows right ventricular hyper trophy and right axis deviation If complete transposition is

Auricular septal defect and the Lutembacher syndrome lead to right sided cardiac enlargement without clubbing or polycythemia and with minimal cyanosis of the tips of fingers and toes A harsh basal systolic murmur with snapping reduplicated second sound over the pulmonary area is the rule with systolic and low pitched *mid* diastolic apical murmurs The ECG shows slight right axis deviation widening of the QRS complex and generally right bundle branch block or right ventricular strain Right sided cardiac enlargement and a small aortic knob with enormous dilatation of the pulmonary artery and a conspicuous hilar dance are evident on x ray in the Lutembacher syndrome Such patients are highly susceptible to respiratory infections rheumatic fever and cardiac arrhythmias Prophylactic chemotherapy or antibiotics are recommended Relative longevity is the rule and surgery is not yet successful enough to justify closure of auricular defects

Ventricular septal defect causes a harsh systolic murmur and thrill in the midsternal region with a normal appearing heart and generally normal ECG pattern Such patients are asymptomatic and require no treatment other than that generally recommended in cardiac malformations

Cyanotic congenital heart disease generally places a strain on the right side of the heart Exercise usually increases the cyanosis by contrast when cyanosis is due to inability to oxygenate the blood in the lungs the inhalation of oxygen increases cyanosis Cyanosis in early infancy is generally due to direct shunting of venous blood into the systemic circulation (e g complete transposition of great vessels) cyanosis which becomes apparent in early childhood is usually caused by a venous arterial shunt from the right to the left auricle (as in Ebstein s disease) cyanosis which develops shortly after puberty is often associated with pulmonary hypertension (as in the Ei enmenger complex) The volume of pulmonary blood flow can be estimated by the vascularity of the lung fields

In the tetralogy of Fallot there are early cyanosis and clubbing The second pulmonic sound is weak there is generally a basal systolic murmur and thrill The pulmonary conus is concave and the ECG shows right axis deviation and right ventricular hypertrophy The more intense the

cases The chief value of angiocardiography in this anomaly is to differentiate an atypical case from rarer conditions

In two cases of transposition of the great vessels the aorta was demonstrated to arise from the right ventricle and form the right cardiac border Overfilled lung fields and en larged pulsatile main pulmonary arteries were shown

Five patients with pure pulmonary stenosis were observed and a localized stenosis was seen in four of them Absence of early filling excluded an overriding aorta Angiocardiography was therefore useful in distinguishing this form of stenosis from the tetralogy of Fallot In eight cases of pulmonary steno sis with interatrial communication the interatrial shunt was demonstrated to differentiate this condition from the tetral ogy Pulmonary atresia (single outflow tract) a term used by the authors to describe any malformation in which the main blood supply to the lungs is from the aorta can be differenti ated from the tetralogy of Fallot by angiocardiography which can also demonstrate the actual derivation of the pulmonary blood supply

Tricuspid atresia produces a typical angiocardiogram with a conspicuous triangular clear area where the right ventricle is located Here again the angiocardiogram gives important information about the origin of the pulmonary blood supply

In Ebstein s anomaly (displacement of a maldeveloped tri cuspid valve into the right ventricle) the angiocardiogram shows an enormous right auricle other features are poor visualization of the right ventricle and pulmonary arteries and poor filling of the lungs together with displacement of the tricuspid valve to the left

The demonstration of the site and extent of coarctation of the aorta is of great help preoperatively and can be achieved in most cases

Angiocardiography is of little help in the diagnosis of pulmonary hypertension with central cyanosis (Eisenmenger s syndrome atrial septal defect with reversed shunt or patent ductus arteriosus with reversed shunt) It is of no help gen erally in establishing the presence of an uncomplicated atrial eptal defect or patent ductus arteriosus

Oximetry in Congenital Heart Disease with Special Ref erence to Effects of Voluntary Hyperventilation Normal sub jects show a rise in arterial oxygen *saturation as measured*

combined with pulmonary stenosis systemic pulmonary anastomosis and creation of an auricular septal defect may help

In truncus arteriosus there are persistent cyanosis and a continuous murmur over the lungs This murmur resembles that in patent ductus arteriosus but seldom produces a thrill X ray reveals a slightly to moderately enlarged heart but no fulness of the pulmonary conus The large truncus arteriosus arches to the right or the left at an abnormally high level If the pulmonary blood flow is severely reduced a Blalock Taussig operation may be beneficial

Pulmonary hypertension with persistent patent ductus arteriosus (reversed ductus) is often associated with malformations of the left side of the heart Whenever pressure in the pulmonary artery exceeds that in the descending aorta blood will flow from the pulmonary artery to the descending aorta Consequently the feet will be more cyanotic than the hands If blood is forced back from the pulmonary artery into the ascending aorta the left hand will be more cyanotic than the right Operation is not feasible

General rules on management of patients with cardiac malformations include (1) treating the child as normally as possible (2) prophylaxis with antibiotics before any kind of oral surgery and general avoidance of infections (3) adequate fluid intake for the polycythemic patient (4) in event of paroxysmal dyspnea placing the child in knee chest position and if necessary giving 1 mg morphine/10 lb body weight inhalation of oxygen may help

[Dr Taussig has had a very wide experience with congenital heart disease and this experience is summarized here—Ed]

Critical Analysis of Clinical Value of Angiocardiography in Congenital Heart Disease, based on study of 118 cases is presented by J F Goodwin R E Steiner J P D Mounsey (Postgrad Med School London) A G MacGregor and E J Wayne[2] (Royal Infirm Sheffield)

Tetralogy of Fallot was studied in 42 cases It was found that accurate anatomic information is available preoperatively as regards the position of the aortic arch and its branches the relation of the subclavian to the pulmonary artery confirmation of the presence of both pulmonary arteries and the equality or inequality of filling of the lungs The type and site of pulmonary stenosis was not visualized in a fifth of the

(2) Brit J Radiol 26 161 184 Ap 1 1953

to indicate a reversal of the shunt between the atria caused by marked increase in pulmonary blood flow

The effect of voluntary hyperventilation depends on the presence or absence of pulmonic stenosis or pulmonary hyper tension and the site of the venous arterial shunt If the pulmo nary blood flow cannot be increased there is a less than normal increase of saturation Where a high ventricular septal defect coexists with pulmonic stenosis (tetralogy of Fallot) or pulmonary hypertension (Eisenmenger s complex) the fall in systemic resistance favors increase of the venous arterial shunt and there is a fall in the oxygen saturation

Origin of Left Coronary Artery from Pulmonary Artery Hans Hartenstein (M C U S A) and D Joe Freeman[4] (Univ of Wisconsin) state that this rare anomaly is characterized clinically by progressive dyspnea apparent pain and symptoms of shock after feeding progressive cardiac enlargement par ticularly to the left and failure The ECG generally shows in version of T waves in all three limb leads and low voltage Cyanosis clubbing murmurs and thrills are not noted Pa tients rarely survive the first year of life

In a girl aged 4 months the ECG indicated first degree auriculo ventricular block tendency to left axis deviation inversion of T waves in leads I and II and the T wave inconstantly diphasic in lead III P R interval was 0 14 second Q R interval 0 06 second Dur ing observation the T waves became upright in leads II and III this was attributed to progressive coronary in ufficiency At autopsy the heart weighed 58 Gm There were left ventricular hypertrophy and dilatation endocardial fibrosis and myocardial congestion with hy dropic degeneration The left coronary artery arose from the left posterior sinus of the pulmonary artery and there was an anom alous fold of tissue in the anterior aortic sinus of Valsalva

Infundibulum of Patent Ductus Arteriosus Diagnostic Sign in Conventional Roentgenograms Gunnar Jonsson and Georg Fredrik Saltzman[5] (Stockholm) point out that the commonest roentgen feature of patent ductus arteriosus— dilatation of the pulmonary artery—is demonstrable in 50 75% of cases The only lesions pathognomonic of patent ductus arteriosus demonstrable on conventional x rays are calcium deposits in the ductus these however are rare and were de monstrable in only 2 of 39 cases of patent ductus arteriosus In 21 of the 39 conventional posteroanterior x rays showed a

(4) A M A Am J D Ch ld 83 774 781 J 195
(5) A t d 1 38 8 16 J ly 195

by the oximeter during strenuous voluntary hyperventilation This is due to the net effect of factors favoring the increased uptake of oxygen and the increased utilization of oxygen Preliminary observations indicate that in normal subjects systemic peripheral resistance is lowered during voluntary hyperventilation since the cardiac output is increased proportionately more than the mean systemic blood pressure

E van Lingen and Joanna Whidborne[3] (Univ of Witwatersrand) report oximetric readings on 30 individuals with congenital heart disease including atrial septal defect high ventricular septal defect Eisenmenger s complex isolated pulmonic stenosis without septal defects tetralogy of Fallot pulmonic stenosis with intact interventricular septum and patent foramen ovale Ebstein s anomaly with patent foramen ovale and patent ductus arteriosus Congenital heart disease associated with a left to right shunt (atrial septal defect or uncomplicated patent ductus arteriosus) demonstrates a normal response to hyperventilation In congenital heart disease with a right to left shunt one or more of the following observations can be made arterial oxygen unsaturation at rest abnormal reduction in saturation during exercise diminished response to oxygen administration In addition if pulmonary resistance is relatively fixed as in pulmonic stenosis and in some cases of pulmonary hypertension there will be a less than normal increase in oxygen saturation after hyperventilation In patients with pulmonic stenosis and intact interventricular septum and patent foramen ovale (not permitting any left to right shunt) there are negligible changes in arterial saturation In the presence of a high ventricular septal defect and pulmonic stenosis (tetralogy of Fallot) or a high interventricular septal defect with pulmonary hypertension (Eisenmenger s complex) there is an increase in shunt from right to left and a decrease in oxygen saturation The procedure appears of value in differentiation of tetralogy of Fallot from pulmonic stenosis with intact interventricular septum and patient foramen ovale Ebstein s anomaly associated with patent foramen ovale on the other hand shows a marked fall in arterial saturation during exercise and a normal response to hyperventilation This has not been found in any other type of cyanotic congenital heart disease and is presumed

(3) Circulation 6 740 748 Nov 1952

the branching more clearly Intravenous angiocardiogram clearly showed the abnormal pulmonary vein Cardiac catheterization was unsatisfactory so far as demonstrating the possible existence of an atrial septal defect

The clinical significance of partial anomalous venous return is not usually considered great However there may be serious consequences when a disease process incapacitates the normally draining lung tissue Although a lung with partial venous drainage is a potential hazard it should not be considered as simply a burden on the right heart The oxygen uptake from the lung probably represents an emergency reserve

If all pulmonary veins enter aberrantly into the right heart a septal defect must be present generally interatrial If this defect is sufficiently large the patient may have few symptoms In the four cases of total aberrant drainage into the left innominate vein the x ray picture was characteristic All patients had diminished arterial oxygen saturation The ECG s showed incomplete right bundle branch block in two instances

Asymptomatic Isolated Valvular Pulmonary Stenosis Diagnosis by Clinical Methods S Gilbert Blount Jr Seuchi Komesu and Malcolm C McCord[7] (Univ of Colorado) discuss the clinical recognition of isolated pulmonary valvular stenosis with intact interventricular and interauricular septa This anomaly considerably more common than heretofore realized has been found in 21 of the authors patients Six patients aged 5 14 are reported on

Diagnosis was correctly made in all by clinical methods No patient had limitation of activity or any symptoms of cardiovascular dysfunction all had history of a discovery of a murmur All patients were well developed There was no cyanosis or clubbing A systolic thrill was palpable along the left sternal border in five patients it was of greatest intensity in the first or second interspace or both A harsh systolic murmur (grade 3 6) was heard over a similar area transmitted poorly to the carotid arteries There was definite diminution in intensity on descending the left sternal border thus when the murmur was most intense in the second interspace it was considerably louder in the first interspace than in the third The second pulmonary sound was diminished or absent in all and was never split

Fluoroscopy showed the lung fields to be abnormally clear

(7) New England J Med 248 511 J 1 1953

definite deformation of the aortic shadow at the site of the infundibulum of the ductus where the aortic arch becomes continuous with the descending aorta This aortic irregularity was not found in comparative studies on 50 physically healthy subjects [In most patients the normal concavity noted where the arch passes over into the descending aorta was replaced by a slight convexity leaving the illusion that the transition be tween arch and descending aorta was displaced down In 12 additional patients with patent ductus and concomitant coarc tation of the aorta the sign was not demonstrable Although this sign may sometimes be obscured—with a large thymus greatly distended pulmonary artery or thorax deformity—it is considered strong evidence of isolated patent ductus arterio sus

Clinical Diagnosis of Anomalous Pulmonary Venous Drainage is discussed by H A Snellen and F H Albers[6] (Univ Hosp Leiden) Pulmonary venous drainage may be partially or totally anomalous In cases of partial abnormal drainage from the literature the usual sites into which the pulmonary veins emptied were found to be the superior vena cava right atrium and left innominate vein In cases of total anomalous drainage the pulmonary veins entered the supe rior vena cava coronary sinus right atrium left innominate vein and portal vein Total anomalous drainage has a poor prognosis In only 13 of 56 reported cases was survival time more than eight months Partial abnormal venous return is tolerated considerably better

The authors report one case of partial anomalous drainage with the right pulmonary vein emptying into the inferior vena cava and four of completely abnormal venous return with drainage into the left innominate vein all of which were di agnosed clinically Diagnosis could be made in every case by cardiac catheterization and in three by angiocardiography The conventional chest x ray is characteristic in patients with total drainage into the left innominate vein showing a figure of eight shadow

Woman 21 with partial anomalous venous return was not cy anotic and complained only of dyspnea and chest and back pain X ray examination showed a rather broad abnormal vascular shadow parallel to the right lower cardiac border which appeared to branch into the upper lung field A planigraphic film demonstrated

(6) C   lation 6 801 816 Dec mb   1952

was noted in most tracings X ray study showed the right ventricle enlarged in all patients The main pulmonary artery was prominent in 22 There was a disproportionate enlargement of the left root shadow in 17 and 20 were considered to have normal peripheral vascular markings and 3 decreased markings Cardiac catheterization was performed on 17 patients and in all the point of stenosis was considered to be valvular rather than infundibular Right ventricular pressure was *elevated in 16 No evidence of other cardiac lesions was found*

Surgery was done on 11 patients 2 had a dissection type pulmonary valvulotomy and 9 a Brock valvulotomy The five patients with adequate follow up have benefited symptomatically from the operation Right ventricular pressure was determined postoperatively in two and in both it was considerably reduced

Because the life expectancy of the patient who is not operated on is jeopardized nonsurgical therapy is not generally adequate Evidence of pronounced symptoms considerable cardiac hypertrophy and increased right ventricular pressure are indications for operation Patients with minimal symptoms and little or no change on tests can probably be safely observed until the long term results in patients who have had surgery have been evaluated

Fallot s Tetralogy Its Differentiation from Pulmonic Stenosis with Intact Ventricular Septum and Interauricular Communication (Fallot's Trilogy) M McGregor B van Lingen T H Bothwell J Kaye J Greenstein Joanna Whidborne J L Braudo H D Jacobs and G A Elliott[9] report data based on seven cases of the tetralogy of Fallot and five of the trilogy Electrocardiography phonocardiography radiologic *examination and cardiac catheterization were carried* out in all cases and angiocardiography in five Additional information was obtained at surgery in five cases and at autopsy in four Oximetric tests were made in nine In three cases of tetralogy an additional defect of an interatrial communication with right to left shunt was present

No obvious or consistent differences were found in the clinical histories although cyanosis tended to develop later in life in the trilogy No constant differences were found in the apical impulse A weak systolic thrust and diastolic shock

(9) S th Af J Cl S 3 154 170 S pt be 195

in two patients normal in the others The main pulmonary artery was increased in size in all and there was a dispropor tionate increase in pulsations of the main pulmonary artery with normal or decreased pulsations in the right and left pul monary arteries In only two patients was there fluoroscopic or ECG evidence of right ventricular hypertrophy Cardiac catheterization performed in all showed an abrupt increase in systolic pressure as the catheter was drawn back from the pulmonary artery into the right ventricle the pressure of which was elevated in all

These patients may have no symptoms until the disease is far advanced In order best to utilize surgical remedies diag nosis must be made early Pulmonary stenosis can be differ entiated from interventricular septal defect by the higher loca tion of the murmur A thrill is unusual in a patient with inter auricular septal defect whereas it is almost always present in the patient with isolated pulmonary stenosis In the differen tiation of subaortic and aortic stenosis from pulmonary steno sis the quality of the murmur the thrill and the qualities of the second heart sound may be of limited value because of the similarity of these findings however fluoroscopy and ECG should establish the correct diagnosis Idiopathic dilatation of the main pulmonary artery generally does not cause the harsh systolic murmur of pulmonary stenosis

Congenital Pulmonary Stenosis without Cyanosis John J Galligan Forrest H Adams and Joseph Jorgens[8] (Minne apolis) point out that isolated pulmonary stenosis is probably not as rare a lesion as previously considered Review of data on 23 patients with noncyanotic pulmonary stenosis showed that onset of symptoms was slow and that no symptoms ap peared before early childhood Ten patients were asymptomat ic The typical complaint was exertional dyspnea three pa tients had precordial pain on exertion There was no history of squatting as is typical in the tetralogy of Fallot nor was there clubbing of the digits A loud pulmonary systolic mur mur was present in all patients and with one exception the second pulmonic sound was depressed There were no diastolic murmurs Electrocardiograms of 22 patients were available 19 had axis deviation greater than 90 degrees Right ventricu lar hypertrophy was present in 18 and peaking of the P waves

(8) J Ped at 41 56 573 No embe 195

Electrocardiogram in Tetralogy of Fallot Arnold Woods[1] (Guy s Hosp) analyzed the ECG in 52 cases of this anomaly and compared them with the usual standards for diagnosis of right ventricular hypertrophy Evidence of right ventricular hypertrophy was found in all There was reversal of the ratio of the amplitudes of R and S in the chest leads occurring most frequently in lead V_1 where R was greater than S in 98% In the other case there was unusual rotation and backward tilting of the apex There was a delay in onset of the intrinsic deflection to 0 03 second in 94% In an analysis of the tetralogy of Fallot Donzelot *et al* found the differential index between the intrinsic deflections in leads V_6 and V_1 to negative or zero in all of 100 cases In the present series the differential index was negative or zero in 96% A qR complex was present in eight cases The fact that death occurred in all eight suggests a correlation of this finding with poor prognosis The T wave was inverted in lead V_1 in 73% of cases it extended beyond lead V_1 in only 15% Since inversion of T waves often extends far across the left chest in severe pulmonary stenosis with right to left interatrial shunt the relatively restricted area of T wave inversion found in the tetralogy may be of diagnostic value There were two cases of incomplete bundle branch block otherwise the QRS complex was of normal duration throughout Often in right ventricular hypertrophy the R wave in lead aVR is prominent This was found in 68% of the cases Abnormally tall pointed P waves were found in 35% of cases and there was evidence of pronounced right axis deviation in both standard and unipolar limb leads in 98%

In 7 of 15 cases in which autopsy was done the right ventricle was measured In all there was evidence of marked right ventricular hypertrophy but there was no correlation between anatomic hypertrophy and the ECG evidence for this as measured either by the height of the R wave or the R/S ratio in lead V_1

Marfan s Syndrome Observations at Necropsy with Special Reference to Medionecrosis of the Great Vessels Hsi Lin Tung and Averill A Liebow (Yale Univ) consider an impor

(1) B t H rt J 14 193 203 Ap 1 195
(2) Lab In t 1 38 406 Fall 195

were present in four cases of tetralogy and were probably due to the fact that the aortic root is closer to the chest wall with dextroposition This sign may be useful in differentiating tetralogy from conditions without dextroposition It occurred in only one case of the trilogy and was probably due to an enlarged right ventricular outflow tract as the patient was acyanotic and had functionally a pure atrial septal defect The pulmonic second sound was not split in any case of severe pulmonic stenosis it was obviously split in two cases of mild pulmonic stenosis

No differences were found in the phonocardiographic records of the two groups The ECG showed the presence of right bundle branch block in two cases of the trilogy This finding has been reported by others but has not been observed in tetralogy Prominence or concavity of the pulmonary artery segment is the principal radiologic point of differentiation in the two anomalies It has been suggested that the degree of prominence of the segment varies with the site of stenosis With the infundibular stenosis so frequent in tetralogy there is hypoplasia of the pulmonary vessels and the pulmonary arc is concave in the trilogy, valvular stenosis is commonly found and is often associated with poststenotic dilatation and prominence of the pulmonic arc However exceptions to this generalization are frequent When present associated vascular abnormalities are probably indicative of tetralogy as anomalies of the large vessels are quite uncommon in the trilogy

The site of pulmonary stenosis could be accurately determined by cardiac catheterization but because the loci of stenosis are not consistently different in the two congenital anomalies this information is only suggestive Only when the catheter tip can be passed into the left auricle or up the aorta from the right ventricle can the site of the septal defect be determined Immediate filling of the left atrium in angiocardiography indicates reversed interatrial shunt whereas in the tetralogy there is early aortic filling without left auricular opacification The presence of associated congenital vascular anomalies may also be demonstrated by angiocardiography Oximetry during hyperventilation shows increased unsaturation in the presence of ventricular septal defect but little or no change is found in its absence

Phenolic Compounds in Treatment of Rheumatic Fever I Study of Gentisic Acid Derivatives Many phenolic compounds have been demonstrated to have antirheumatic properties including salicylic acid amatin o cresotinic acid m cresotinic acid gentisic acid gamma resorcylic acid and salicyl resorcinol Little is known about the mechanism of action of these drugs or compounds but it is probably related to the following properties (1) antihyaluronidase activity (2) blocking action on systems due to oxidation reduction properties (3) possible adrenocortical action and (4) effect on allergic processes due to their ability to precipitate or combine with certain proteins Gentisic acid has been demonstrated to be a metabolite of salicylic acid and its compounds have been shown to have very desirable antirheumatic effects as compared with salicylates—increased tolerance with little or no toxic manifestations and probable heightened effectiveness Norman E Clarke Robert E Mosher and Charles N Clarke[3] (Providence Hosp Detroit) report on 44 patients with rheumatic fever treated with the following gentisic acid compounds (1) sodium gentisate (2) sodium gentisate combined with an anion resin (3) sodium gentisate 0 3 Gm mixed with methyl cellulose 0 09 Gm in tablets and (4) gentisic acid ethanolamide

Sodium gentisate 1 or 1 2 Gm every three or four hours day and night was given to 13 patients with primary attacks of rheumatic fever As improvement occurred the dosage was gradually reduced to a minimum of 1 2 Gm four times daily Symptomatic relief occurred within the first two weeks in most patients and the sedimentation rate was normal within an average of four weeks Evidences of cardiac damage (murmur enlargement) regressed in several patients Fifteen patients with recurrent attacks of rheumatic fever were given 5 2 10 4 Gm sodium gentisate every 24 hours at 3 hour intervals Average duration of treatment was six months Twelve have remained symptom free for an average of eight months since treatment was discontinued Evidences of heart damage decreased generally

Sodium gentisate was combined with an anion resin in an attempt to delay rapid elimination (which necessitated frequent medication) and to bind the sodium an undesirable

(3) Circulation 7 247 257 February 1953

tant but underemphasized feature of Marfan s syndrome to be loss of elastic tissue or medionecrosis in the aorta or pulmonary artery or both Two fatal cases are reported in which this lesion was present It was also found at 9 of 20 autopsies in previously reported cases and was frequently associated with a dissecting aneurysm The authors first patient aged 40 months is the youngest on record with a notable defect in the elastic tissue of the aorta Medionecrosis of the root of the aorta is commonly extensive enough to result in aneurysmal dilatation The deformity of the valve cusps by this dilatation may lead to aortic insufficiency—a clinical feature in several of the fatal cases in adults—and death in congestive heart failure has supervened Aortic or pulmonary insufficiency does not usually result from medionecrosis not associated with Marfan s syndrome

Medionecrosis of the pulmonary artery was present in the authors second patient a man aged 35 This resulted in probable aneurysmal dilatation of the artery with pulmonary insufficiency and right ventricular hypertrophy Although there was loss of elastic tissue in the aorta as well it was not so extensive as in the pulmonary artery and there was no aortic aneurysm

Six of the 22 patients with Marfan s syndrome were under age 4 years Four had cardiac hypertrophy and two had congestive heart failure The cause of death in all was pneumonia Among the 16 patients over age 5 dissecting aneurysm was the cause of death in 6 in 4 congestive heart failure was associated with dissecting aneurysm The other two patients had bacterial endocarditis

The features of Marfan s syndrome are tendency to great height arachnodactyly clubbing of the feet bony spurs looseness of the joints scoliosis kyphosis spina bifida funnel chest pigeon breast dolichocephaly frontal bossing deep set eyes high palate dental abnormalities especially elongated teeth muscular weakness scanty subcutaneous fat lenticular subluxation and deformities cataracts irregular pupils iridodonesis miosis coloboma defects in the cardiac septa valvular thickening and medionecrosis These features should be searched for in every patient with dissecting aneurysm Medionecrosis should be considered as a possible pathogenic mechanism in aneurysms of the pulmonary artery

In a three year study of the distribution of these substances in plasma David P Barr Ella M Russ and Howard A Eder[4] (New York Hosp Cornell Med Center) confirmed observations that in most pathologic states the lipids are chiefly distributed between fraction IV + V + VI (as alpha lipoproteins) and fraction I + III (as beta proteins) Early in the study a difference in distribution of cholesterol in the plasma of young men and women was demonstrated In young women the percentage of cholesterol as alpha lipoprotein was higher and that as beta lipoproteins lower than in young men After age 45 there was little difference in distribution between the sexes In patients who had survived severe myocardial infarctions the percentage of cholesterol as alpha lipoprotein was low and that as beta lipoprotein was correspondingly elevated

To discover if the presence of circulating estrogens might affect the distribution of cholesterol daily doses of estrogen equivalent to 10 000 R U were given to 16 men and 2 women with advanced atherosclerosis The men were aged 22 57 and all had had one or more myocardial infarctions The women were aged 48 and 54 one had had an infarction and the other had hypercholesteremia and xanthelasma In every patient there was an increase in the percentage of cholesterol in the form of alpha lipoproteins and a reduction in beta lipoproteins Concentration of total plasma cholesterol was also reduced but less constantly than the distribution Plasma neutral fat concentration often elevated in atherosclerotic subjects was variably affected After three or four weeks the dose caused considerable breast development and temporary loss of sexual drive and potency

The physiologic and clinical significance of these changes is not known but one may speculate on the possible stabilizing influence of an agent such as estrogen

Estrogen Induced Regression of Coronary Atherosclerosis in Cholesterol Fed Chicks. Ruth Pick Jeremiah Stamler Simon Rodbard and Louis N Katz[5] (Michael Reese Hosp) studied the effect of estrogen on cholesterol induced coronary atherosclerosis in chicks

METHOD —Fifty 1 day old chicks were fed commercial mash until

(4) T A Am Ph 65 102 113 1952
(5) C cul t 6 858 861 D mbe 1952

cation in the treatment of patients with congestive failure The preparation was generally unsuccessful in the treatment of five patients This experience indicates that the compound reduces the effect of sodium gentisate

Methyl cellulose sodium gentisate tablets were given to four patients with primary rheumatic fever and two with recurrent attacks Dosage was 8 Gm daily portions being given every three hours during the day Sedimentation rate returned to normal in an average of 28 days The advantages of this preparation are the heightened activity as compared with sodium gentisate and prolonged effect as a result of lower urinary output

The most successful results were with gentisic acid ethanolamide given to five patients (three with primary attacks) Dosage was 1 Gm every three hours six times daily Sedimentation rate became normal in an average of 25 days Subsequent examination showed distinct regression of signs of cardiac damage No toxic reactions occurred The preparation is more effective than sodium gentisate and lacks the sodium ion

Of the entire series of patients 39 had a rise in lymphocyte count (average 54%) and 4 a fall In all 23 of the patients so studied there was a greater than 50% decline in the absolute eosinophil count with a fall to zero in 4 patients The lymphocyte elevation is not characteristic of adrenocortical stimulation The decline in eosinophils constitutes corroborative evidence of previously postulated participation in the adrenocortical pituitary axis

No toxic reactions have been observed although single doses of as much as 6 Gm and prolonged treatment with as much as 5 2 Gm daily for 24 months have been used

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CORONARY ARTERIOSCLEROSIS

√ **Influence of Estrogens on Lipoproteins in Atherosclerosis** Women during the childbearing age are relatively immune to myocardial infarction and other complications of atherosclerosis After the menopause this advantage is lost Concentrations of cholesterol phospholipids and total lipids are approximately equal in the plasma of young men and women

groups and a high transmethylation activity Unlike such lipotropic agents as methionine choline and inositol it is completely free from toxic effects The lipotropic action results from its ability to donate methyl groups for synthesis of choline or methyl transfer in the liver

Twenty one patients with coronary atherosclerosis and myocardial infarction or angina pectoris of exertion were given up to 12 Gm betaine/day (average 6 Gm) orally for six months ages ranged from 41 to 70 years (average 53) 14 were men They had all been on low fat low cholesterol diets and had had intensive lipotrope therapy consisting of 6 Gm choline base or 3 Gm choline base combined with 3 Gm inositol a day The patients consistently reported increased well being increased exercise tolerance reduced cardiac pain and decreased exertional dyspnea Improvement in the bio chemical abnormality was constant Laboratory studies showed that the average total serum cholesterol level before treat ment was 274 6 mg and after treatment 314 mg /100 cc Average serum phospholipid level before treatment was 270 mg and after treatment 281 mg /100 cc (normal 175 375 mg) The serum phospholipid cholesterol ratio averaged 0 99 before treatment and 1 24 after treatment (normal 1 0 3 0) An important factor in lipotropic action is the ability of the lipotropic agent to contribute methyl groups which com bine with lipids to form phospholipids increase in the phos pholipid cholesterol ratio is therefore indicative of lipotropic activity

Consistent clinical and laboratory evidence of improve ment in atherosclerosis particularly in patients showing maxi *mal response to other lipotropic agents* is considered highly significant

Further Studies on Relationship of S_f 10 20 Lipoprotein Molecules to Atherosclerosis are reported by Thomas P Lyon Hardin B Jones Dean M Graham John W Gofman Frank T Lindgren and A Yankley[7] (Univ of California) The concentration of this lipoprotein fraction in the blood of presumably normal persons has been found to parallel the clinical incidence of atherosclerosis in such persons The level is generally higher in patients with proved myocardial infarc tion or with angina pectoris It is higher in diabetic patients

(7) A M A A h I t M d 89 4 1-4 7 M rch 195

age 7 weeks then a high cholesterol diet (2% cholesterol plus 5% cotton seed oil in mash) was administered At the end of five weeks on this formula 10 birds were killed all had coronary artery and aortic atherosclerosis which in this study is considered to mean presence of lipid in any layer of the vessel wall with or without lipophage or fibroblastic activity The other 40 birds were then divided into four groups of 10 each These groups were paired and the birds of one group of each pair were given 1 mg estradiol benzoate intramuscularly every day The first pair was killed at age 15 weeks the second at 20 weeks Twenty sections of the coronary arteries were studied sudan IV hematoxylin eosin and van Gieson s stains being used Regression of coronary lesions was considered established by the presence of fibrosis with little or no associated lipid deposit

In all birds with or without estrogen treatment athero sclerosis was found in the aorta Estrogen apparently had no effect on the process In contrast however there was con siderable difference in the estrogen fed chicks and the controls with regard to the coronary arteries Controls killed at 15 weeks showed a high percentage of coronary vessels with atherosclerosis with no evidence of spontaneous regression In the estrogen fed birds killed at 15 weeks the lesions were smaller and showed a predilection for the media and adventitia seeming to spare the intima There was an even more striking difference in the birds killed at 20 weeks Three estrogen fed birds were entirely free from atherosclerotic lesions in the coronary vessels and the other estrogen fed birds showed considerable regression 100% of the controls showed coronary atherosclerosis with a high degree of coronary involvement

The mean values for total plasma cholesterol were similar in the groups before estrogen was administered After estrogen therapy there was a pronounced rise in the plasma phospho lipid and a moderate increase in plasma cholesterol

√ The results of these studies support the thesis that athero sclerosis is a reversible lesion even to the extent of clearing fibrosis from the vessel wall The mechanism of estrogen induced regression of coronary lesions is obscure It may be that estrogen decreases permeability of the endothelium for lipids induces lipophage activity or alters the plasma lipo proteins

Results of Betaine Treatment of Atherosclerosis Lester M Morrison[6] (Los Angeles) reports on the mechanism of action of betaine a choline like compound with three methyl

(6) Am J D g t D 19 381 384 Dec mbe 195

utilized It is based on addition of a constant amount of heparin to the blood and titration of the sample with protamine Although the nature of all factors affecting protamine titer is uncertain the substances thereby measured are characterized by two properties (1) they influence blood coagulation and (2) they are combined with protamine to form compounds which are inactive in the coagulation process

Of 55 patients 27 had atherosclerosis without myocardial infarction or with *no myocardial infarction during the preceding three months* 4 had fresh myocardial infarction and 24 were considered normal and were of an age range comparable with the others These 24 were considered normal because they had no clinical evidence of atherosclerosis although autopsy has shown a high incidence of atherosclerosis in clinically normal individuals

The protamine binding capacity was lower in the athero sclerotic patients than in the normal persons and each group showed decrease in titer with increasing age

This reduction in protamine binding in atherc cl rosis may be due at least in part to a decrease in the heparinoid sub stances of the blood The four patients with fresh myocardial infarction all showed an *incr ase* in the protamine titer and this was correlated with the previously repor ed increase in mucoproteins following myocardial infarction presumably a result of tis ue destruction Reduction of blood heparinoids may constitute one factor in the pathogenesis of human athero sclerosis

Hematopericardium Complicating Myocardial Infarction in Absence of Cardiac Rupture Report of Three Cases Hematopericardium severe enough to cause cardiac tamponade has previously been noted after anticoagulant therapy Only one of the three patients discus ed by Milton W Anderson Norman A Christensen and Jesse L Edwards[9] (Mayo Clinic) was being treated with anticoagulants Two patients who died of the complication had no evidence of cardiac or coro nary rupture at autopsy but both had gross extravasation of partly clotted blood in the pericardial ac and organizing fibrinous pericarditis with hemorrhage into the granulation tissue associated with a transmural infarction In one the extravasation into the pericardial exudate coincided with the

(9) A M A A h I t M d 90 634-645 N embe 19

manifesting vascular disease than in those without overt vascular disease

A representative group of 100 patients with previous myocardial infarction who had been followed for 12 18 months but had had no recurrence was compared with 26 similar patients who had recurrent myocardial infarction over the same period The average blood level of the S_f 10 20 molecules and the frequency of high levels were found to be statistically significantly greater in the patients with recurrent infarction

Low fat low cholesterol dietary management of patients with coronary artery disease was effective in reducing average S_f 10 20 levels This reduction was associated with a definite reduction in the rate of occurrence of new myocardial infarctions

Parenteral heparin therapy consistently has reduced the incriminated lipoprotein fraction Thirty of 32 patients with angina pectoris had dramatic reduction of this symptom for 3 10 days after intravenous injection of 25 100 mg heparin The general effect could be prolonged by use of repository heparin

[There is some uncertainty as to whether the presence of S_f 10 20 lipoprotein molecules in excess amount is or is not more significant than the total blood cholesterol A number of recent publications fail to substantiate the beneficial effects of use of heparin in patients with angina pectoris —Ed]

Blood Heparinoid Substances in Human Atherosclerosis Addition of coagulation active lipid to a protein solution has previously been demonstrated to enhance the heparin binding capacity of protein In addition to heparin there are heparinoid substances in the blood which are responsible for 99% of the anticoagulant activity of the blood they are for the most part acid polysaccharides including (in addition to the heparin itself) the phosphotungstic acid precipitable mucoprotein fraction of the serum E A Nikkila and S Majanen[8] (Univ of Helsinki) undertook to ascertain the extent to which occurrence of abnormal lipoproteins and human atherosclerosis (as demonstrated by Gofman *et al*) is based on a possible decrease in blood heparin and heparin like substances (heparinoids)

Inasmuch as the heparin content of blood is extremely small the indirect protamine titration method of Allen was

(8) Scand av J Clin & Lab Invest 4 204-210 1952

position and can occur with almost any disease or in persons in whom no disorder is found In the authors experience this type of pain is never cardiac

Pains occurring in the midline or symmetrically across the chest are likely to be related to heart disease the farther from the midline a unilateral pain occurs the less likely it is to be cardiac pain occurring outside the nipple line is not caused by heart disease Skeletal pains may begin on the left side of the chest and go down the left arm However when pain occurs across the epigastrium and progresses down the arm it is nearly always cardiac or diaphragmatic as from a hiatus hernia A chest pain going to the neck jaws or teeth is almost always from heart disease The hyperesthesia which accompanies coronary artery disease pain—angina or coronary infarction—has a duration measured in minutes to days never months or years as happens frequently with nerve root pain Angina requires an approximately fixed degree of exertion and time to be induced neuritic and arthritic pains simulating angina do not occur with a regular amount of exercise and with the constancy that angina does

In differentiation of cardiospasm heartburn and other gastrointestinal epigastric pain from cardiac infarction the history often shows a relation to meals certain foods alcohol or tobacco excess or a tension state Alimentary pains are often preceded by a water brash which rarely occurs with angina Eructation itself however may occur in angina as well as gastric pain because the vagal reflex present in many cases of angina produces regurgitation of gas Pain from alimentary sources usually remains localized in the epigastrium and is often burning in character cardiac pain may begin under the xiphoid process or lower but nearly always radiates up over the chest to one or both arms Pressure over the gall bladder may produce left inframammillary pain

The chief importance of extrasystoles is that they frighten patients and engender a cardiac neurosis Auricular tachycardia although not of itself evidence of myocardial disease may become important as an aggravation when it occurs in damaged hearts

Effort syndrome (soldiers heart neurocirculatory asthenia etc) is characterized by precordial pain palpitation on little effort inability to breathe properly on physical exertion

area of infarction in the other the pericarditis over the infarcted myocardium was not hemorrhagic but hemorrhage was mainly into the granulation tissue over the diaphragmatic surface removed from the infarcted anterior wall of the left ventricle

Patients with extensive myocardial infarction particularly those with pericardial friction rub and especially if they are receiving anticoagulants should be carefully observed for signs of pericardium Hematopericardium when suspected requires prompt anticoagulant neutralizing measures if anti coagulants have been used Pericardial paracentesis may be lifesaving when there is cardiac tamponade from hemato pericardium without a cardiac rupture

Pain or Distress Wrongly Attributed to the Heart is dis cussed by John A Oille and William A Oille[1] (Univ of To ronto) Careful inquiry and symptom reproducing procedures aid greatly in correct diagnosis of symptoms wrongly attrib uted to the heart Most patients who consult a physician for evaluation of discomfort which they impute to heart disease are suffering only from fear of heart disease a fear often inadvertently instilled by a physician s ill considered remark These patients need positive reassurance that their hearts are sound and in order to make this statement with conviction it will generally be necessary to explain the genesis of all the patient s symptoms to him as accurately as possible

Submammary and axillary pains are frequently considered indicative of heart ailment by the anxious patient Spondylitis usually causes unilateral pain variable in location intensity frequency duration and character Pain from spondylitis and other musculoskeletal pains are often worse in particular postures and may be produced and duplicated by some particu lar movement Dermatomic distribution of these pains is not a reliable criterion since the pains may follow interspaces or go directly across them bearing no relation to nerve segments Sometimes particularly accompanying cord tumor extruded intervertebral disk or spinal osteoarthritis the nerve root pain has very constant characteristics Skeletal pains are often described as shooting or stabbing either as isolated stabs or a series of sharp jabs Although the cause of this pain is difficult to ascertain it is usually related to movement or body

(1) M Cl North Ame a 36 501 513 Ma ch 195

position and can occur with almost any disease or in persons in whom no disorder is found In the authors experience this type of pain is never cardiac

Pains occurring in the midline or symmetrically across the chest are likely to be related to heart disease the farther from the midline a unilateral pain occurs the less likely it is to be cardiac pain occurring outside the nipple line is not caused by heart disease Skeletal pains may begin on the left side of the chest and go down the left arm However when pain occurs across the epigastrium and progresses down the arm it is nearly always cardiac or diaphragmatic as from a hiatus hernia A chest pain going to the neck jaws or teeth is almost always from heart disease The hyperesthesia which accompanies coronary artery disease pain—angina or coronary infarction—has a duration measured in minutes to days never months or years as happens frequently with nerve root pain Angina requires an approximately fixed degree of exertion and time to be induced neuritic and arthritic pains simulating angina do not occur with a regular amount of exercise and with the constancy that angina does

In differentiation of cardiospasm heartburn and other gastrointestinal epigastric pain from cardiac infarction the history often shows a relation to meals certain foods alcohol or tobacco excess or a tension state Alimentary pains are often preceded by a water brash which rarely occurs with angina Eructation itself however may occur in angina as well as gastric pain because the vagal reflex present in many cases of angina produces regurgitation of gas Pain from alimentary sources usually remains localized in the epigastrium and is often burning in character cardiac pain may begin under the xiphoid process or lower but nearly always radiates up over the chest to one or both arms Pressure over the gall bladder may produce left inframammillary pain

The chief importance of extrasystoles is that they frighten patients and engender a cardiac neurosis Auricular tachycardia although not of itself evidence of myocardial disease may become important as an aggravation when it occurs in damaged hearts

Effort syndrome (soldiers heart neurocirculatory asthenia etc) is characterized by precordial pain palpitation on little effort inability to breathe properly on physical exertion

area of infarction in the other the pericarditis over the infarcted myocardium was not hemorrhagic but hemorrhage was mainly into the granulation tissue over the diaphragmatic surface removed from the infarcted anterior wall of the left ventricle

Patients with extensive myocardial infarction particularly those with pericardial friction rub and especially if they are receiving anticoagulants should be carefully observed for signs of pericardium Hematopericardium when suspected requires prompt anticoagulant neutralizing measures if anti coagulants have been used Pericardial paracentesis may be lifesaving when there is cardiac tamponade from hemato pericardium without a cardiac rupture

Pain or Distress Wrongly Attributed to the Heart is dis cussed by John A Oille and William A Oille[1] (Univ of To ronto) Careful inquiry and symptom reproducing procedures aid greatly in correct diagnosis of symptoms wrongly attrib uted to the heart Most patients who consult a physician for evaluation of discomfort which they impute to heart disease are suffering only from fear of heart disease a fear often inadvertently instilled by a physician s ill considered remark These patients need positive reassurance that their hearts are sound and in order to make this statement with conviction it will generally be necessary to explain the genesis of all the patient s symptoms to him as accurately as possible

Submammary and axillary pains are frequently considered indicative of heart ailment by the anxious patient Spondylitis usually causes unilateral pain variable in location intensity frequency duration and character Pain from spondylitis and other musculoskeletal pains are often worse in particular postures and may be produced and duplicated by some particu lar movement Dermatomic distribution of these pains is not a reliable criterion since the pains may follow interspaces or go directly across them bearing no relation to nerve segments Sometimes particularly accompanying cord tumor extruded intervertebral disk or spinal osteoarthritis the nerve root pain has very constant characteristics Skeletal pains are often described as shooting or stabbing either as isolated stabs or a series of sharp jabs Although the cause of this pain is difficult to ascertain it is usually related to movement or body

(1) M Cl North Am a 36 501 513 Ma h 195

on the slightest discomfort Diagnosis of angina pectoris is essentially clinical and does not totally depend on ECG or other laboratory findings

Chest wall pain arising in the musculoskeletal tissues can develop during exercise and is often confused with angina Procedures which generally reproduce such pain are compression of the chest in the anteroposterior direction as well as in the lateral direction with careful finger tip pressure to all points of the chest wall and in particular the costochondral junctions fist percussion of the chest and cervical and dorsal spine manipulation of the arms and shoulder girdle simulating that occurring during walking walking with the arms held rigidly to the sides movement of the chest and arms in all directions with and without resistance and procaine block of superficial structures Procaine block is not specific and may relieve not only skeletal pain but pain arising in the heart as a consequence of myocardial ischemia

Hyperventilation a frequent result of anxiety concerning chest pain may itself cause chest pain which is either bilateral or (at times inexplicably) unilateral Reproduction of such pain is best done during routine auscultation of the chest while the patient is urged to breathe maximally This may take several minutes

Hiatal hernia cardiospasm and malformations of stomach and esophagus may cause angina like pain in the chest More frequent are chest pains due to aerophagia and gastric distention or distention of the splenic flexure In such cases there is often a history of instantaneous relief by eructation or expulsion of flatus Distention of the stomach with air by Levin tube or of the splenic flexure of the colon by rectal tube (often requiring 1 000 1 500 ml air) is a simple way to reproduce these types of pain The patient should be placed in the sitting position for several minutes and palm pressure applied over the distended organ

Demonstration that a given pain is aggravated by respiratory maneuvers practically excludes angina pectoris

The pain which most closely mimics angina pectoris is pulmonary hypertensive pain or hypercyanotic angina It is precipitated by effort but demonstration of intrapulmonary disease or evidence of right ventricular strain and failure of

and fatigue Sighing often occurring in functional disease must be distinguished from dyspnea Fatigue is said to be the hallmark of the psychoneurotic These patients need strong reassurance they often are true psychoneurotics and are very difficult to cure

[Most errors in the interpretation of chest pain arise from one of two causes overemphasis by the physician of the significance of minor ECG changes or a failure to question the patient carefully about his pain and the exact conditions which cause it By and large the history is the single most valuable tool in the interpretation of cardiac pain and in the differentiation of coronary disease from innocent disorders which may mimic it The location of a pain in the chest is less important than its behavior In patients with myocardial infarction the ECG will usually show definitive changes However in persons with angina pectoris normal resting records are the rule Even after exercise the ECG changes are often no different from those seen in many normal subjects Any attempt to substitute rule of thumb methods for a complete history and a thorough physical examination is likely to lead to errors in the interpretation of chest pain

Another point in this paper which merits emphasis is the statement about the importance of anxiety and of reassurance Anxiety is the most important symptom in many patients who have organic heart disease In many instances such patients are suffering not so much from the heart disease as from their anxiety concerning it Alleviation of unnecessary anxiety is of the utmost importance in managing patients with cardiac disease —Ed]

Diagnostic and Therapeutic Value of the Reproduction of Chest Pain is considered by T J Reeves and T R Harrison[2] (Med College of Alabama) Anxiety is becoming the most important of all symptoms of persons with cardiac disease or with the suspicion of cardiac disease Chest pain is often related by the patient to serious heart disease Erroneous interpretation of noncardiac pain as an omen of sudden death is responsible for mental suffering and invalidism and it is important to reassure the patient Reproduction of chest pain by the examining physician is therefore not only of diagnostic but of therapeutic value

The diagnosis of angina pectoris is generally dubious unless it meets two criteria (1) the pain should be reproducible by physical effort under appropriate conditions as regards emotional stress meals etc and (2) it should be demonstrated that the same physical effort carried out under the same conditions does not cause the pain when undertaken a few minutes after administration of glyceryl trinitrate The mode of inducing physical effort is of secondary importance but it must be constant The exercise must be discontinued instantly

(2) A M A Arch Int Med 91 8 5 Jnary 1953

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glyceryl trinitrate to increase exercise tolerance are important in differential diagnosis

In all maneuvers designed to reproduce noncardiac chest pain the essential requirement is that the pain must be exactly reproduced in quality and location although the intensity will be variable When these time consuming procedures do demonstrate that the pain is not from heart disease the patient's relief from terrifying apprehension fully justifies the time spent

Esophageal Contraction and Cardiac Pain William Evans[3] (London Hosp) states that pain similar to that of myocardial ischemia brought on by effort and relieved by rest in a patient with a normal ECG may be the result of esophageal arrhythmia In this fluoroscopically demonstrable condition the barium bolus temporarily halts at the diaphragmatic opening while still held there by a spastic cardia subsequent swallows of barium progressively distend the lower esophageal segment then perhaps by retroperistalsis a portion of the entrapped barium is regurgitated These irregular movements differ from the fluoroscopic appearance of cardiospasm

In a group of controls consisting of 700 healthy subjects 200 patients with painless heart disease and 500 with ECG evidence of cardiac infarction esophageal arrhythmia was present in 2 6% The sign occurred in 1 3% of the 900 patients without chest pain and in 5% with cardiac infarction whose pain was presumed to be the direct outcome of coronary artery disease A test series consisted of 332 patients who complained of chest pain subjectively characteristic of cardiac pain but had no ECG evidence of coronary artery disease Every patient had previously been told that he had cardiac pain and many had been treated for this condition The pain was usually in the center of the chest and was described as gripping constricting a tightness a sense of pressure or aching—never lancing Often it radiated to the jaw shoulder or left arm In 114 of these patients the pain was only brought on by exertion and quickly relieved by rest in the others the pain occasionally developed during rest and/or lasted an hour or more suggesting cardiac infarction In none of these patients was there evidence of heart disease Esophageal arrhythmia could be seen fluoroscopically in 40% of the test series The

(3) Lancet 2 1091 1097 Dec 6 1952

majority of the 332 patients had been followed for over 2 years and 15 for as long as 10 years Five patients later had an abnormal ECG which in one instance could be correlated with development of aortic stenosis In only 4 of the 332 patients the author feels was the chest pain caused by coronary artery disease in the presence of a normal ECG In none of these patients unfortunately was the ECG previously reported normal repeated after exercise

Of the 14 deaths among the 332 patients during the period of follow up only 1 was due to heart disease Of 1 000 patients with true cardiac pain examined during the same period 190 had died 184 of cardiac infarction

Both the mechanism of esophageal arrhythmia and the pain which may or may not accompany it are in dispute however spasm does not engender the pain because when spasm occurred under fluoroscopic observation it was not accompanied by pain Exhaustive searches for ulceration herniation gall bladder disease and other causes for pain were not carried out However it is important that in this select group of patients the pain was of a cardiac nature not caused by swallowing The pain can be relieved by glyceryl trinitrate octyl nitrite or amyl nitrite and sometimes by more specifically gastrointestinal remedies including carminatives

Prevention of Thromboembolism in Acute Coronary Artery Disease Good risk patients with myocardial infarction have such low mortality and low incidence of thromboembolic complication that the risk of decreased coagulability of the blood induced by anticoagulants may exceed the dan er of thrombo embolism David Littmann[4] (V A Hosp West Roxbury Mass) reports results of a plan of treatment in 169 consecutive patients with acute coronary artery disease In addition to nonmedicinal prophylactic measures anticoagulants (heparin and dicumarol®) were used only in patients considered to be poor risk (i e age over 60 history of earlier myocardial infarction evidence of congestive failure persistent shock intractable pain or high fever history of previous thrombo embolism auricular fibrillation peripheral vascular disease and phlebitis or thrombosis) Nonmedicinal measures generally used in all patients included limited sedation encourage

(4) New Eng J Med 247 05 08 Aug 7 1952

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Clinical Use of Nor Epinephrine in Treatment of Shock Accompanying Myocardial Infarction and Other Conditions is discussed by George S Kurland and Monte Malach[5] (Beth Israel Hosp Boston) Nor epinephrine (aminoethanol cate chol) produces generalized arterial capillary and venous vaso constriction with an increase in total peripheral resistance and a resultant increase in systolic diastolic and mean systemic arterial blood pressure The cardiac output is decreased and the pulse rate is decreased The pulmonary circuit exhibits a pressor effect similar to the systemic circuit Splanchnic blood flow is not significantly changed Coronary vasodilatation has been reported In contrast epinephrine increases the systolic systemic blood pressure but has a variable effect on diastolic pressure The total peripheral resistance is decreased and the cardiac output and pulse rate are both increased Blood flow to the splanchnic area is increased

Fourteen patients with shock accompanying acute myo cardial infarction and 16 with shock accompanying various other pathologic states were treated with nor epinephrine 37 infusions being used in the entire series Nor epinephrine was diluted in 1 000 cc of 5% glucose or 0 85% saline to yield a solution for intravenous administration containing 5 μg /ml The flow was regulated to elevate the systolic pressure to about 100 mm Hg A pressor effect was observed in 30 of the 37 courses of treatment Abrupt withdrawal of nor epinephrine was often accompanied by sudden hypotension generally obviated by gradual cessation of therapy Duration of treat ment varied from 10 minutes to 6 days

Acute pulmonary edema occurred immediately after admin istration of nor epinephrine in one instance and readily responded to the usual treatment Intense vasospasm phle-bitis and skin ulcerations over the recipient area occurred in 14 patients This was decreased by use of hot packs above the needle site Complete healing occurred in all instances

[In patients with acute myocard al infa ction and circulatory collapse d gitalis is often the most valuable agent in treatment and this is particu larly true if there are s gns of pulmonary edema or if the patient is dysp-neic In general nor-epinephrine and related compounds are to be pref rred to transfusion but they should not be considered a substitute for digitalis —Ed]

(5) N w E gl d J M d 247 383 389 S pt 11 1952

ment of activity in bed bathroom privileges for all except the very ill and early ambulation

Of 25 deaths 13 occurred in the first 48 hours after hospitalization Some of the 13 patients had anticoagulant therapy and in others urgency of the disease precluded such treatment Autopsies done on 12 showed no evidence of thromboembolic disease Of 156 patients who survived 48 hours or longer anticoagulants were used in 44 Seven died one of cerebral hemorrhage which was considered to be due to the anticoagulant therapy No evidence of thromboembolism was found at autopsy Of the 112 patients who were not treated with anticoagulants 5 died Three were poor risk patients who could not be given anticoagulants for various reasons There was no evidence of thromboembolism

In surviving patients pulmonary infarction occurred in six of whom four were receiving anticoagulants Of the two who were not one was a poor risk patient with history of peptic ulcer who was not given anticoagulants for this reason and the other was an apathetic individual who was less active than desirable Two patients had arterial emboli one was receiving anticoagulant Seven patients had cerebrovascular accidents five were receiving anticoagulants

Source of most complicating venous thrombosis is considered to be the leg veins a phenomenon related to stasis There is no strong evidence that anticoagulant drugs influence in any degree development of mural thrombi over sites of myocardial infarction For these reasons the author strongly urges early ambulation and exercise of the legs Elevation of the head of the patient s bed on 10 in blocks promotes an awkward position for the patient encouraging frequent change of position largely involving leg muscles

The author concludes that anticoagulant therapy should be reserved for patients with acute myocardial infarction who show evidence of congestive failure prolonged shock intractable pain or high fever or who will be expected if they recover to be confined to bed for long periods Efficacy of anticoagulants in these patients is unquestioned in less seriously ill persons however added risk of hemorrhagic complication and secondary expense involved generally make anticoagulant therapy undesirable

drug in taste and appearance was substituted No other medication was given during treatment with veriloid® or placebo except occasionally atropine banthine® a low cholesterol diet and in seven patients digitalis for congestive heart failure

Only 27 patients showed a sustained fall in systolic pressure of 10% or more of the control value No apparent relationship was evident between the initial diastolic pressure and results obtained with veriloid® Side effects were the limiting factor in dosage and included particularly nausea and vomiting In no cases were normal blood pressure levels reached No improvement was noted in retinal changes ECG s or heart size Although 23 patients had subjective improvement in the symptoms attributed to hypertension there was no correlation demonstrable between subjective response and change in blood pressure

Veriloid® is at best a palliative in treatment of ambulatory patients with essential hypertension the therapeutic advantage being seriously limited by the annoying side reactions

[At the present time the available evidence indicates that the combination of hexamethonium and hydrazinophthalazine (apresoline®) is probably the most generally satisfactory method of lowering blood pressure in most patients who require any type of specific therapy This type of management has certain drawbacks The drugs often have unpleasant side effects and the blood pressure must be followed at frequent intervals if they are to be used Despite these disadvantages the combination of hexamethonium and hydrazinophthalazine appears to be the most effective specific drug therapy Many pat ents need no blood pressure lowering drugs and are best handled by regulation of living particularly with regard to avoiding emotional stress —Ed]

Arterial Hypertension—Therapeutic Effect of Cation Exchange Resins Robert J Gill and Garfield G Duncan[8] (Jefferson Med College) present a study based on the premise that some patients with essential hypertension are salt sensitive and will receive benefit from rigorous dietary sodium restriction and that an ammonium potassium carboxylic cation exchange resin (in this study resodec) facilitates maintenance of the low sodium diet particularly in the nonhospitalized patient Thirty eight patients each with diastolic pressure of at least 100 and with moderately good renal function were allowed 1 2 Gm /day sodium intake and were given 15 Gm resodec three times daily after meals with 2 Gm calcium lactate and 2 3 Gm potassium citrate daily added later as adjunctive treatment Salt substitutes were permitted After

(8) N w E gl nd J Med 247 271 276 A g 21 1952

Treatment of Hypertension with Oral Protoveratrine S W Hoobler R W Corley T G Kabza and H F Loyke[6] (Univ of Michigan) evaluate the dosage program and review their clinical experience with protoveratrine a purified derivative of Veratrum album which they found useful in long term treatment of severe hypertension whatever its origin For satisfactory results the following dosage program must be followed The initial dose is large (0 5 1 5 mg) and given orally after breakfast a reinforcing dose (0 25 mg) is given at 10 a m and another (0 25 mg) after lunch (1 p m) The drug is always taken after meals or not less than 1½ hours before the next meal On this schedule the emetic effects are kept subthreshold and hypotensive concentrations are attained Veriloid® one of the Veratrum viride derivatives also studied provoked nausea and vomiting if given in doses sufficient to lower blood pressure Side effects with protoveratrine are by contrast minimal with the proper dosage schedule

Significant daily reductions in blood pressure lasting six to eight hours, were secured in most patients The drug is particularly useful in treatment of left ventricular failure Relief of hypertensive headaches and encephalopathy and restoration of vision in malignant hypertension are notable beneficial effects Protoveratrine s particular usefulness is in alleviating symptoms and lowering blood pressure in patients for whom surgery or dietary treatment is unsuccessful or inapplicable It is used in palliative rather than curative management of hypertension

Clinical Experiences with Veratrum Alkaloids (Veriloid®) in Prolonged Treatment of Hypertension Alfred A Bolomey and Rosemary Lenel[7] report results in 50 patients with blood pressures in excess of 140/90 After a control period the patients were given 3 8 mg veriloid® daily in divided doses The dose was gradually increased to tolerance For most patients the maximal well tolerated dose could be established in several weeks and averaged 11 8 mg daily Therapy wa continued for 5-48 weeks then a placebo identical to the

(6) Ann Int M d 37 465 481 S pt mb r 195
(7) Perman nte F u d M B ll 10 57 68 Aug st 1952

lor Univ) Fifty eight patients were given hexamethonium chloride orally for 4 16 months The initial dose was 250 mg four times daily given before each meal (to decrease rate of absorption) and at bedtime This amount was increased stepwise until an adequate response was obtained (reduction of 20 mm Hg in the mean blood pressure) or until side effects forced discontinuance of the drug Excessive variation in blood pressure between doses of hexamethonium in some patients necessitated giving the drug at more frequent intervals

All but 11 patients had an adequate drop in blood pressure without severe side effects but in seven the response was unstable or otherwise unsatisfactory Apresoline® was added to the regimen of these 18 patients in an initial dose of 25 mg four times daily with increases in 25 mg increments at weekly or semiweekly intervals Seven of the patients who did not respond originally fared no better on the combined therapy the other four and the seven with unsatisfactory control by hexamethonium alone had good results from the combined therapy Altogether 60% of the patients treated could be satisfactorily maintained on hexamethonium alone Blood pressure returned to 150/100 or less in 47% of patients

The amount of drug required to reduce the blood pressure was apparently not dependent on the height of blood pressure elevation Patients with concurrent cardiac failure or malignant hypertension were more difficult to regulate Concomitant severe renal disease made therapy more precarious and more difficult In general the patients with ECG evidence of left ventricular strain reacted well those with the ECG pattern of myocardial damage showed little response The outstanding symptomatic improvements were relief of hypertensive headaches and angina pectoris occurring in three fourths of the patients with these complaints There was no evidence that tolerance to the drug developed

Side effects which forced stopping treatment before significant reduction in blood pressure was obtained included urinary retention severe constipation weakness nausea and vomiting or diarrhea or excessive variability of the blood pressure Side reactions were generally ascribable to the mild curare like effect parasympathetic ganglionic block or excessive hypotension and orthostatic syncope Reflexes responsible for adjusting peripheral vascular resistance are blocked

two to five months of this regimen the resin was replaced by a placebo which consisted of a tablet containing the resin together with the amount of sodium it would theoretically remove in vivo (1 or 2 mEq/Gm) In some instances addition of 4 Gm enteric coated sodium chloride tablets to the resin program was used rather than substitution of a placebo and in some patients the placebo was given initially and resodec subsequently

Confirming previously established claims greatest hypotensive effect was closely associated with lowest urinary sodium levels particularly in cases in which values were consistently below 0 5 Gm daily Of nine patients considered to have achieved optimal response—attaining a reduction of at least 20 in diastolic pressure and reduction of diastolic pressure to 100 or below—eight were receiving 1 1 25 Gm sodium daily Addition of salt to the diet consistently elevated blood pressure and exacerbated the symptoms Improvement on the resin low sodium diet regimen was not limited to diminution in blood pressure in some patients headaches and nervousness decreased hypertensive retinopathy regressed ECG patterns became more nearly normal ballistocardiographic patterns were considered to have improved and renal function became better

Complications of resin therapy include electrolyte imbalances (in particular hypopotassemia) which can be controlled by assiduous maintenance of constant intake and addition of prophylactic calcium and potassium salts Since the absorptive capacity of the resins decreases after several days of use and return to previous levels is slow after discontinuance of treatment intermittent administration of the resins is suggested *Hypotensive effect of dietotherapy and resins may be slow in* appearing and patients should be kept on this regimen for two months before being considered insensitive

By facilitating sodium restriction in ambulatory patients with good renal function resin therapy is considered to have an important place in treatment of hypertension

Results with Oral Hexamethonium Alone and in Combination with 1 Hydrazinophthalazine (Apresoline®) in Therapy of Hypertension are reported by John H Moyer Harvey B Snyder Ira Johnson Lewis C Mills and Sam I Miller[9] (Bay

(9) Am J M Sc 2 5 379 398 Ap il 1953

venous pyelography and the examination repeated if one kidney apparently fails to excrete the dye If unilateral disease is suspected from intravenous pyelography and normal renal function catheterization of ureters and individual kidney function tests should be done If the disease is unilateral nephrectomy may be expected to relieve the hypertension in about half the cases Should the disease be bilateral nephrectomy is generally contraindicated Hypertensive neuroretinopathy is an imperative sign for reduction of blood pressure In unilateral cases where nephrectomy has failed or in bilateral cases additional procedures which may be resorted to are hexamethonium compounds parenterally subtotal adrenalectomy and sympathectomy

Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone III Control of Hypertension with Cortisone Hypertension is uncommon in the adrenogenital syndrome although it is frequent in Cushing's syndrome Lawson Wilkins John F Crigler Jr Samuel H Silverman Lytt I Gardner and Claude J Migeon[2] (Johns Hopkins Univ) present three cases of congenital adrenal hyperplasia with hypertension In all small doses of cortisone lowered the blood pressure and maintained it at normal levels for 14 24 months Overdosage induced hypertension perhaps on the basis of sodium retention Inadequate suppression of adrenal cortical hyperplasia as demonstrated by the urinary 17 ketosteroid level was related to failure to reduce the elevated blood pressure

The histologic site chemical nature and mode of action of the pressor factor of the adrenal cortex are unknown Adrenal resection in one of the patients demonstrated hyperplasia of the zona glomerulosa Patients with congenital adrenal hyperplasia who have a defect of the electrolyte regulation frequently have agenesis of this area There was evidence but not proof that the carbohydrate regulating adrenal corticoids were deficient in this patient The zona fasciculata thought to be the source of adrenal glycogenetic hormones could not be identified in the operative specimen This fact together with clinical evidence of hypoglycemia was indication of the additional metabolic defect

( ) J Cl E d 1 12 1015 1030 A gu t 1952

by hexamethonium and orthostatic hypotension is pronounced. For this reason dosage should be regulated according to the upright blood pressure Any tendency toward an increasing blood urea nitrogen during therapy is a definite contraindication to further reduction in blood pressure

Myocardial ischemia can result from the tachycardia consequent to lowering of the blood pressure This may occur with apresoline* If the sympathomimetic cardioacceleratory action of this drug is previously blocked with hexamethonium which is a ganglionic blocking agent then it can be a valuable adjunct in treatment of hypertension

Nephrectomy and Other Treatment for Hypertension in Pyelonephritis G W Pickering and R H Heptinstall[1] (St Mary s Hosp) report results of nephrectomy for hypertension in 11 patients One had unilateral renal tuberculosis four had bilateral pyelonephritis and seven had unilateral pyelonephritis with no clinical or radiographic evidence of disease in the opposite kidney Postoperative condition was observed up to 10 years in all but one patient the follow up period was at least 5 years

In four of the seven patients with unilateral pyelonephritis persistent relief from hypertension was obtained one of these had hypertension in the malignant phase In all the other patients the operation was unsuccessful It is suggested that the three patients with unilateral disease who were unrelieved by surgery may have had involvement of the opposite kidney undiagnosable by clinical methods The malignant phase of hypertension was relieved by subtotal adrenalectomy (7/8 removal) in two children who had obtained no relief with nephrectomy In the six patients with reduction of hypertension by nephrectomy with or without subtotal adrenalectomy the postoperative blood pressure remained slightly or considerably above the normal level

Unilateral pyelonephritis may cause hypertension and yet be asymptomatic with no more than a trace of albuminuria and with normal renal function Every patient with malignant hypertension and every patient over 40 with severe hypertension not due to coarctation of the aorta Cushing s syndrome or chronic glomerulonephritis should be examined by intra

(1) Quart J Med 22 1 2 Jan y 1953

system stimulation with adrenolytic activity and has particular use as a test agent in diagnosis of hypertension due to excess circulating adrenaline nor adrenaline from a pheochromocy toma False positive results are extremely rare but results may be negative in the presence of a pheochromocytoma possibly due to superimposition of secondary vascular changes on a pheochromocytoma induced hypertension which tend to perpetuate it independent of the original tumor A test done of 10 mg F 933/sq m of body surface was given intravenously over a two minute period in the diagnostic survey of 300 hypertensive patients and 100 normotensive persons One patient had a significant drop in blood pressure lasting three minutes in three tests with F 933 but the test was considered indecisive because the hypotension was unsustained Other workers have shown that such a response may be indicative of a pheochromocytoma with sufficient circulating pressor substance to break through the F 933 blockade

Mild side effects in 99% of the hypertensive subjects and all of the normotensive persons consisted generally of a sen sation of warmth of face and neck tension sighing respiration and tachycardia the production of tachycardia is one of the few adrenaline actions in the body not blocked by F 933 In three hypertensive subjects side effects were unpleasant and were primarily those of apprehension and alarm Six patients with a history of hypertensive encephalopathy had no recurrence of symptoms and in 12 persons with moderate angina and 10 others with old myocardial infarction the drug was used with impunity Contraindications were cardiac failure and recent myocardial infarction Otherwise F 933 may be used as an essentially innocuous drug in the routine investi gation of hypertensive patients

CARDIAC SURGERY

Surgical Treatment of Aortic Stenosis According to C P Bailey H I Redondo Ramirez and H B Larzelere (Hahne mann Med College) aortic stenosis a rare valvular lesion generally produced by rheumatic fever may also be congenital or arteriosclerotic in origin In arteriosclerotic aortic stenosis

(5) J A M A 150 1 47 165 Dec 27 195

Evaluation of New Adrenolytic Drug (Regitine®) as Test for Pheochromocytoma is presented by Ray W Gifford Jr Grace M Roth and Walter F Kvale[3] (Mayo Clinic and Found) The drug (C 7337) first used by Grimson and his co workers was given to 259 patients of whom all but 20 had hypertension. Seven were found to have pheochromocytomas Criteria for a positive test result were (1) blood pressure drop exceeding 35 mm Hg systolic and 25 mm diastolic or from hypertensive to normotensive (140/90) levels (2) occurrence of maximal depressor effect within 2 minutes after intravenous injection or 20 minutes after intramuscular injection The dose used was 5 mg regardless of the route of administration except in two instances in which 10 mg was given intramuscularly Regitine® had some depressor effect on the blood pressure in 66% of patients with essential hypertension but pressures rarely decreased less than 35 mm systolic and 25 mm diastolic.

False positive reactions were obtained in 3 of the 149 patients without pheochromocytomas who were given regitine® intramuscularly and in 4 of 107 given the drug intravenously These reactions were attributed to (1) sedation before the test (2) uremia and (3) basal blood pressures in the low hypertensive range No false negative reactions were obtained with regitine® intravenously Two patients with pheochromocytomas showed no response to the drug intramuscularly but had a positive response when it was given intravenously

Regitine® is recommended as a screening test for pheochromocytoma because it is safer and pleasanter than piperoxan and can be injected in an instant so that injection and blood pressure recording can be done by one person It does not produce as severe a pressor response in hypertensive patients as may occur with piperoxan Equivocal results do occur and should be evaluated by comparison with other pharmacologic tests Regitine® should not be given in test doses of more than 5 mg In both instances in which 10 mg was given the response was false positive

Application of F 933 as Routine Test in Sustained Hypertension Donald F Gibbs[4] (Royal Infirm Edinburgh) reports on use of F 933 (2 1 piperidylmethyl 1 4benzodioxane) which combines the sympathomimetic qualities of central nervous

(3) J A M A 149 16 8 1634 Aug 30 1952
(4) Edinb gh M J 59 517 529 N mb 1952

before the aortic operation None died and all had excellent results Only one patient showed evidence of aortic regurgitation

When mitral and aortic stenosis occur together both must be corrected at the same operation preferably the mitral lesion first Two patients of another group with aortic stenosis treated with mitral commissurotomy alone died presumably as a result of increased inflow into the left ventricle with a persistent mechanical obstruction to outflow The postoperative aortic orifice need be only 50% of its original size excessive dilatation may cause regurgitation and increase the risk of splitting in the aortic wall

[The brilliant results obtained in the operative treatment of mitral stenosis have naturally led to attempts at surgical treatment of aortic stenosis This problem has proved more difficult and is now being done by relatively few surgeons However the present report leads to the hope that with further advances in technic and with further experience in the proper selection of patients the happy results in patients with mitral stenosis will soon be duplicated in those with aortic stenosis —Ed]

Indications for Commissurotomy in Mitral Stenosis Commissurotomy is designed to reconstruct the stenotic mitral valve surgically without producing mitral insufficiency O Henry Janton Robert P Glover and Thomas J E O Neill[6] (Philadelphia) performed this operation on over 400 patients between 1948 and 1952 with an over all mortality of 10% The greatest single factor in successful surgery is proper selection of patients The authors present their criteria

Progressive easy fatigability is an important prodrome of cardiac failure and patients should be seen by the surgeon no later than at this stage However a mitral diastolic murmur in itself does not at this point justify surgery The older the patient the more rigid the standards for selection Anatomic response to the inciting agent in rheumatic fever may be delayed so that the physiologic age of the mitral lesion may not correlate with the chronologic age of the patient However few operable patients will live beyond the fourth decade or if they do most will have serious and forbidding concurrent cardiac complications

Ideally the mitral lesion should be a pure stenosis without mitral insufficiency or other valve lesions If there is other endocardial disease as well the mitral lesion must be predominant Its predominance is assured by the disease pattern of

(6) Am J Med 12 621 625 J 1952

generally not amenable to surgery there often are calcified cusps without commissural fusion Rheumatic aortic stenosis on the other hand is a product of agglutination of edematous commissures symmetrically or asymmetrically with the resultant orifice located centrally or eccentrically within the fibrotic often calcified valves When the lesion develops unequally in the three commissures the anterior commissure is generally the one first fused subsequently both anterolateral cusps become affixed to each other and a bicuspid valve results Aortic stenosis is generally associated with some degree of regurgitation Medical therapy of congestive heart failure that arises in the heart with aortic stenosis is most discouraging and for this reason a surgical approach has been developed

Should any regurgitation suddenly develop as a consequence of operation on the stenotic aortic valve the cardiac embarrassment is almost always extremely serious and may cause death with cardiac dilatation within a few minutes This is the principal surgical consideration

The authors report on 21 patients in whom surgical correction was attempted One was treated by retrograde passage of a dilating instrument through the carotid artery An eccentric orifice enhanced malposition of the instrument and a sinus of Valsalva was ruptured and the right ventricle entered Mechanical dilatation of the false passage resulted in immediate death

A dilator with three spring propelled blades was used on 12 patients 2 of whom died during the hospital stay one of rapid cardiac dilatation the other of peripheral arterial embolism Two others died within a few days of leaving one of blood stream infection the other of cardiac failure The procedure was considered unsatisfactory because it produced inadequate dilatation and caused traumatic axial traction when the instrument was pulled back and forth through the valve orifice

An instrument resembling Brock s pulmonary valve dilator with three blades instead of two was devised Expansion of the instrument is controlled by the surgeon s manipulation and tends to tear the commissures apart as opposed to the back and forth movement of the other instrument used to cut the stenosed tissue The instrument was used on nine patients six of whom had mitral commissurotomy at the same operation just

before the aortic operation None died and all had excellent results Only one patient showed evidence of aortic regurgitation

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progressive cardiopulmonary impairment a left ventricle of normal size left atrial and right ventricular enlargement right axis deviation or no axis deviation on the ECG and evidence of pulmonary vascular hypertension Fluoroscopy should reveal little or no left ventricular enlargement Extreme enlargement of all chambers is an absolute contraindication as is left axis deviation If there is more than one valve defect the ECG will often help in the selection of patients The better the functional capacity of the patient the more ideal the candidate It should be emphasized that untreated mitral *stenoses result in impairment of the myocardium to the extent* that changes become irreversible However congestive heart failure if controllable is not a contraindication to surgery Evidence of pulmonary hypertension (hemoptysis) constitutes a greater urgency for cardiac surgery Active rheumatic fever or bacterial endocarditis are absolute contraindications

The authors urge selection of patients for mitral commissurotomy at first indication of incapacitation for in this way both morbidity and mortality can be considerably reduced

Clinical Observations in Patients Undergoing Finger Fracture Mitral Valvuloplasty II Electrocardiographic Observations were made by Ralph J Spiegl J Bradley Long (Stanford Univ) and Lewis Dexter[7] (Peter Bent Brigham Hosp) in 24 patients 20 of them women during mitral valvuloplasty Serious arrhythmias producing a clinical effect were uncommon Ventricular and auricular ectopic beats were noted most often (in 24 and 19 patients) These generally reverted with no treatment Tachycardia usually associated with hypotension was encountered and required treatment in 19 patients Significant tachycardia in mitral stenosis requires vigorous treatment the choice being a lowering of cardiac output or elevation of the left auricular filling pressure and thereby the pulmonary vascular pressure The former adjustment may induce shock the latter pulmonary edema Ventricular fibrillation seen in three patients indicated serious operative risk for them

Ventricular ectopic beats or ventricular tachycardia observed in every patient during the actual valvule fracture were generally temporary and required no treatment The authors were impressed by the relative stability of ECG trac

(7) Am J M d 12 631 638 Ju 195

ings during cardiac surgery finding nearly as many effects from extracardiac manipulations (rib spreading endotracheal intubation etc) as from palpation suture or incision of the heart Return to preoperative ECG pattern was complete with in a few hours

Pronestyl 0 2 0 4 Gm intravenously) was effective in treatment of ventricular ectopic beats or tachycardia but not of ventricular fibrillation It caused no hypotension Procaine (1% solution) in the pericardial sac generally suppressed ventricular ectopic beats Prostigmine methyl sulfate (0 25 mg in 1 4 000 solution) intravenously was efficacious in slowing the fibrillating heart No toxic effects were noted Atropine (0 1 mg intravenously) was given successfully to relieve bradycardia during surgery Intracardiac injection of epineph rine and 10% calcium chloride did not help cardiac arrest which caused two deaths

Direct Surgery of Arteriosclerosis In some patients arterio sclerosis is of such a segmental nature that resection of the involved section is a practicable if somewhat temporizing procedure In unusual instances as in one reported by Ormand C Julian William S Dye John H Olwin and Paul H Jordan[8] (Univ of Illinois) direct surgery may be useful Their patient had an isolated arteriosclerotic lesion believed to have been directly due to old trauma overlying an old fracture replace ment of the diseased artery with a blood vessel graft as a venous autograft may be curative in such a situation

Selection of cases is rigid and based largely on aortographic findings Four distinct types of arteriograms have been noted (1) Smooth normal appearing artery continues down to an abrupt point of complete obstruction A number of filled col laterals can be seen and the main channel distal to the region of obstruction at the level where the collaterals re enter has a smooth contour (2) A segment of obstruction shows re filling of the distal portion but the main vessel above and below the point of obstruction shows irregular filling defects suggesting a diseased vessel at the point to which the vein must be anastomosed (3) The filled channel abruptly terminates with collaterals that seem adequate but appear to enter more distant branches in the calf and no filling of the distal femoral or popliteal artery can be visualized Operation is usually

(8) A S g 136 459-474 S ptembe 1952

unsuccessful because no distal vessel is suitable for anastomosis (4) The lumen of the main channel is narrow but completely open and there are multiple irregular filling defect and calcification throughout the length of the vessel Operation here is not considered

In favorable cases particularly in the first category autogenous grafts usually taken from the saphenous vein have proved successful for short periods Sometimes to facilitate anastomosis intimectomy or thromboarterectomy is resorted to in the distal cuffs of the diseased artery

Except in unusual circumstances the value of these procedures cannot be considered lasting as most patients also have arteriosclerotic involvement outside the resected area They are therefore subject to other arterial obstructions elsewhere and to reobstruction of the vessel above and below the site of surgery

Further Observations on Resection of Auricular Appendages John M Beal and William P Longmire Jr[9] (Los Angeles) report experiences with resection of the auricular appendage in seven patients with chronic rheumatic heart disease and auricular fibrillation All had had previous embolic episodes The left auricular appendage was resected in six and the right in one There was *no* operative mortality During follow up for 1 2½ years only one patient had further embolic episodes which were controlled conservatively Two patients died both of congestive failure within four months after operation Autopsy on one revealed mitral valvulitis and stenosis with an organizing mural thrombus of the remaining left auricular appendage and a mural thrombus in the left auricular wall An organizing mural thrombus in the right auricular appendage and a large congenital patent foramen ovale were also noted Permission for autopsy on the other patient who had right auricular appendectomy was not obtained

Removal of the left auricular appendage of patients with auricular fibrillation and rheumatic heart disease appears justified if there is good cardiac compensation as large series of autopsies have demonstrated that this chamber is the source of most emboli The result of resection of the right atrial

(9) W t J S g 60 400 403 Aug t 295

appendage done in one case was discouraging The right auricle was distended and the appendage was not a well defined structure It would appear that pulmonary emboli would originate in the veins of the pelvis and lower extremities with significant frequency in patients with chronic cardiac decompensation

The authors believe that the surgical approach to peripheral embolization is preferable to the inconveniences and hazards of anticoagulant therapy in the patient with well compensated chronic rheumatic heart disease and auricular fibrillation

Hypothermia as Means of Performing Intracardiac Surgery under Direct Vision is described by Brian A Cookson Wilford B Neptune and Charles P Bailey[1] (Hahnemann Med College) who carried out experiments on 11 dogs The purpose of the hypothermia is to reduce metabolism and the oxygen need of the body so that the circulation can be safely stopped for a longer period than is possible with normal temperatures The dogs were anesthetized with pentothal® sodium and fortified with penicillin *ACTH (8 Wilson units)* glucose intravenously and oxygen by respirator By use of a cold chamber the temperature of the animals was reduced to 26 C The chest was opened and 10 ml of 1% procaine hydrochloride injected immediately into the pericardial sac Right ventriculotomy was made and repaired after occlusion of the venae cavae After 12 minutes of caval occlusion the superior vena cava was released and benodaine® (0 8 mg /kg) injected into the right ventricular cavity Gradually the inferior vena cava was unclamped the chest closed and the animal warmed to normal temperature Nine of the 11 dogs survived

In earlier experiments there was a predisposition for ventricular fibrillation to develop The behavior of the heart was similar to that following large doses of epinephrine It was because of this similarity and the supposition that inferior caval blood was receiving increased amounts of adrenal medulla hormone released under the stimulus of hypoxia that benodaine® an adrenolytic drug was given as prophylaxis against ventricular fibrillation Fibrillation occurred but once in the 11 dogs which is considerably less than the anticipated incidence The only dog which fibrillated in this series was

(1) D Ch t 22 45 260 Sept mb 1952

unsuccessful because no distal vessel is suitable for anastomosis (4) The lumen of the main channel is narrow but completely open and there are multiple irregular filling defects and calcification throughout the length of the vessel Operation here is not considered

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(9) West J S g 60 400 403 A g t 195

work or of systolic load In diastolic overloading generally a result of regurgitation the increment of work is equivalent to the increment in diastolic loading

These facts suggest that in systolic overloading a mechanism of compensation a change in oxygen consumption and metabolic conditions are present which differ greatly from those in diastolic overloading Increased work and greater oxygen consumption induce muscular hypertrophy thereby facilitating increased shortening for equal systolic loading and making fiber lengthening unnecessary to maintain output

Systolic overloading of the ventricles is generally accompanied by muscular hypertrophy and little or no evidence of dilatation Common causes of systolic overloading of the left ventricle are aortic stenosis or arterial hypertension of the right ventricle pulmonary stenosis or pulmonary hypertension (as in mitral stenosis and chronic cor pulmonale)

Diastolic overloading of the ventricles as occurs in valvular regurgitations arteriovenous communications and anomalous pulmonary venous return into the right heart usually induces considerable dilatation of the involved ventricle with little hypertrophy When myocardial disease is present diastolic overloading is generally present or supervenes onto systolic overloading

Starling's mechanism is considered to obtain in primary diastolic overloading when higher oxygen consumption of the muscle causes hypertrophy giving rise to an increase in the interval in which an increment in diastolic filling determines an increase in heart work Here it is doubtful that ventricular dilatation could be interpreted as failure However in primary systolic overloading as the overload increases or the myocardial capacity decreases Starling s mechanism comes into operation and ventricular dilatation is evidence of myocardial failure

In instances of primary systolic overloading with a healthy myocardium other compensatory devices are operative and Starling s law is considered unimportant

II —Electrocardiographic data —The authors[3] consider the ECG differentiation and characteristics of systolic and diastolic overloading of the right and left ventricles

Diastolic overloading of the right ventricle often is accom

(3) Am H rt J 43 669 686 M y 1953

one which did not receive benodaine* until after the inferior cava was unclamped Neurologic damage persisted in only one animal

In a subsequent series of 16 dogs some modifications in technic were introduced including digoxin administration and use of vasoxyl* as a pressor agent during surgery There were 14 survivals Five dogs were operated on at 17 C with caval occlusion for 30 minutes Two animals survived

The authors suggest consideration of hypothermia as a technic whereby direct vision cardiac surgery may be performed in human beings

PATHOLOGIC PHYSIOLOGY

Systolic and Diastolic Loading of Heart *I—Physiologic and clinical data*—Evidence differentiating ventricular overloading into systolic and diastolic types is presented by Enrique Cabrera C and Jose R Monroy[2] (Inst of Cardiology of Mexico) who develop the hypothesis that Starling's law of the heart is not universally applicable If the initial (diastolic) length of a muscle remains constant with a varying load it is believed to have a variable after loading or systolic loading since the mechanical diastolic conditions are the same whereas those occurring during systole are modified Here a progressive increase in load determines the amount of work which increases at first then declines Total oxygen consumption and probably cardiac efficiency also increase initially with increasing loads in the innervated heart systolic overloadings caused by elevation of aortic pressure produce some bradycardia thus further increasing cardiac efficiency An increase in systolic loading prolongs isometric systole and reduces the amount of shortening during isotonic contraction the difference between this amount of shortening and that which had developed with a smaller systolic loading would cause incomplete ejection which would in turn be the cause of increased diastolic filling thereby setting Starling's compensatory mechanism into operation However for a considerable period the increment of diastolic filling so produced would be relatively small compared with the increment of

(2) Am H art J 43 661 668 May 1952

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panied early by right bundle branch block This has been observed in tricuspid regurgitation tetralogy of Fallot (blood from right ventricle to the aorta increases venous return to the right side) acute cor pulmonale (causing the right ventricle to fail under sudden pulmonary hypertension) anomalous pulmonary venous return into the right heart femoral arteriovenous fistula, as a secondary consequence to systolic overloading and during Muller s test in normal subjects The conduction defect is considered to be functional (e g by attenuation of the Purkinje myocardial junction by stretching) because it is often transitory

Systolic overloading of the right ventricle increases the voltage of the R wave and may cause a negative T wave in lead V_1 It can be demonstrated in pulmonary stenosis patent ductus arteriosus with high pulmonary pressure and occasionally secondary to mitral stenosis The high R wave is probably the result of ventricular hypertrophy The T wave changes are considered not due to ischemia because there is no clinical evidence for this the S T segment is depressed instead of being elevated and the changes can appear when total coronary blood flow increases while left ventricular work decreases (ligation of patent ductus arteriosus or arteriovenous aneurysm) The negativity of the T wave would indicate that the monophasic electric systole of the fibers affected by systolic overload increases its voltage and duration

Diastolic overloading of the left ventricle produces elevation of both R and T waves in the left ventricular potentials This has been observed in rheumatic aortic insufficiency (although a low T wave generally occurs in syphilitic aortic disease probably due to other factors) and after Brock s operation for the tetralogy of Fallot whereby a diastolic left ventricular overloading is produced

In systolic overloading of the left ventricle the most important ECG feature is a flattening or negativity of the T waves and depression of the S T segments in the left ventricular leads similar to systolic overloading of the right ventricle

Respiratory Acidosis Its Relationship to Cardiac Function and Other Physiologic Mechanisms is discussed by Fletcher A Miller, Ernest B Brown Joseph J Buckley Frederick H Van Bergen and Richard L Varco[4] (Univ of Minnesota)

(4) S rg ry 3 171 183 August 1952

Respiratory acidosis previously recognized as a common occurrence during anesthesia was confirmed and documented by the authors who demonstrated that in major operations 35% of patients undergoing general anesthesia experience an alveolar CO tension at least twice normal during some period of the operation Clinical detection of this hypercapnia is difficult it can occur with normal oxygen tension and without cyanosis

Exposing dogs to high CO tension for four to six hours induced a lowering of the arterial blood pH to as low as 6 7 and caused a pronounced bradycardia and increased T wave voltage on ECG Blood pressure was generally maintained at control levels or slightly higher In another series dogs were able to inhale 70% CO for 45 minutes before hypotension developed Concentrations above this were accompanied by hypoxia which was avoided in an attempt to make the experiments more critical Hypovolemia as a result of hemorrhage or other debilitations lowered tolerance to hypercapnia

Rapid restoration of the normal arterial pH and lowering of the hypercapnia by hyperventilation with air or oxygen after chronic exposure to 30% CO consistently caused ventricular fibrillation subsequent to variable ECG changes the most frequent of which was prolongation of the QRS complex Only 4 of 19 dogs survived and in only 1 was no ECG abnormality noted Hypotension regularly accompanied the post hypercapneic ECG abnormalitie and the authors believe that it potentiates the myocardial damage consequent to sudden pH rise or decrease in alveolar CO tension Experiments are in progress to evaluate the role of hypotension as well as the contribution if any of hyperkalemia

Clinical occurrence of cardiac arrest during the period of CO blowoff following administration of general anesthesia lends support to these observations and clearly indicates the necessity for adequate pulmonary ventilation during anesthesia

Ballistocardiography I Physical Considerations Maurice B I appaport Howard B Sprague and William B Thompson[5] (Massachusetts Gen l Hosp) consider the physical principles which govern the response of body movements to cardiovascular forces and how these principles affect the ballistocardio

(5) C cul 7 9 46 F bru y 1953

graphs in use The ballistocardiograph (which records motion with only one degree of freedom) merely registers the body movements produced by the projection of the instantaneous spatial vector along the head foot axis and performs according to the laws of vibration mechanics The recorded curve is the result of the harmonic vibration of the human body with or without the effect of the recording table on which are super imposed the motions produced by cardiovascular forces

The Starr table is designed to vibrate at a relatively high frequency with no specific damping mechanism For an individual of average weight this frequency is about 9 c With such a system there is an increasing response as the applied frequency (i e frequency of cardiovascular forces) approaches the natural frequency of the table Above this point of resonance the response again falls off Thus there is little response to low frequency applied forces such as respiration There is a varying response to the applied cardiovascular forces since these forces contain components between 1 and 10 c As a result of the rising frequency response in the working range the error of differentiation is introduced This manifests itself by recording false negative waves following positive waves Errors in timing may be the result of phase shift which is the lag of the deflection behind the applied force This increases as the ratio of the applied frequency to the natural frequency approaches unity Another objection to any ballistocardiographic table is that no matter how securely the subject is clamped to the table there is still relative motion between subject and table

The Nickerson table is a low frequency critically damped instrument With it there is a falling response with increases in applied frequency and practically no response above 4 c Because of the drooping frequency response characteristic three forms of distortion are introduced (1) reduced amplitudes of complexes (2) increased duration of complexes (3) phase displacement As a result of the excellent low frequency response of the Nickerson table respiratory movements are recorded with such amplitude that respiratory weave presents a major problem

With the Dock technic ballistocardiograms are recorded directly from the body thus eliminating the problem of relative movement between body and table However the natural

frequency of the body falls in the spectral region of the ballistic frequency components Therefore as is the case with the indirect methods the frequency response curve is not flat The degree of damping also varies with the individual body characteristics and with variations in the recording surface The best technic is that which produces the highest natural frequency and maximal damping

Instrumental characteristics may also introduce distortion into the recorded ballistocardiogram A system consisting of a coil of fine wire moving in relation to a magnetic field records velocity and has a rapidly rising frequency response in the working range In the original Dock Taubman magnetic ballistocardiograph the presence of a hinge constituted a serious mechanical defect but this was later eliminated The introduction of a 50 microfarad capacitor equalizing shunt produces a frequency response curve which approaches pure displacement in the working frequencies The larger the capacitor the more completely this is accomplished The photoelectric cell type transducer produces a displacement tracing but when a series condenser is added to eliminate respiratory weave distortion is introduced The piezoelectric crystal transducers depend on their property to generate electric voltages when squeezed or twisted Such a crystal acts as a generator with a condenser in series with it The generated curve is a displacement type which is distorted by a differentiation effect Special circuit design is necessary to prevent this A photoelectric cell transducer with a resistance capacitance type parellel T network attenuator to minimize respiratory weave without significant differentiation is recommended

Calibration of the Starr and Nickerson ballistocardiographs is by application of a longitudinal static force Since frequency response of these tables is not flat such a procedure is meaningless Dynamic calibration procedures should likewise be treated with extreme caution Gross estimates of relative amplitude may be made by maintaining uniform instrumental sensitivity and comparing the size of the recorded complexes from one individual to another

[Investigations of the past few years make it probable that the ballistocardiograph will eventually be an instrument of great practical value However at present, the recording techniques are far from perfected Conclusions concerning the clinical state on the basis of ballistocardiograms should be made with great caution When a subject with an apparently normal heart displays an abnormal ballistocardiogram one should be

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known of their heart disease for less than five years tended not to return to work whereas those who had known of their diseased hearts longer were likely to return Those who did not return to employment were often those whose jobs required most physical effort Patients with more favorable functional classifications generally continued to be employed

Employment did not appear to deteriorate functional or therapeutic classification as in 25% of those employed and in 29% of the unemployed status became worse Cardiovascular episodes—acute rheumatic fever myocardial infarction congestive failure or cerebral accident—occurred in 30% of the employed and in 35% of the unemployed Age rather than employment was apparently the more significant factor in the progression of heart disease

It is concluded that the study provides no evidence that continued employment affects the course of heart disease adversely

[Too frequently physicians advise patients with cardiac disease to cease work Better advice would be to avoid work or other activities which induce shortness of breath pain in the chest or excessive fatigue There is no convincing evidence that in persons with chronic cardiac disease physical activity which can be carried on without the production of symptoms is harmful Obviously this statement does not apply to individuals with acute disorders of the heart such as rheumatic fever and recent myocardial infarction The physician should be careful to avoid inducing economic catastrophe and unnecessary anxiety by advising a patient to cease work It is usually better to allow the patient to continue his occupation provided he can live below the threshold of symptoms Worry and anxiety often cause greater load on the heart than does mild physical exercise —Ed]

Problems in Management of Refractory Heart Failure

Because some cases of intractable heart failure represent incomplete or erroneous diagnosis or management Charles K Friedberg and Mark Halpern[8] (Mount Sinai Hosp New York City) suggest a systematic survey of contributory factors

1 Is the diagnosis of congestive heart failure accurate? Among important differential diagnoses to be considered and excluded are pulmonary disease carcinomatosis anemia hepatic and renal disease

2 Is there a remediable contributory constituent? Recognition and adequate treatment of hyperthyroidism which may be responsible for precipitating congestive heart failure may lead to a dramatic recovery in previously unresponsive failure Beriberi anemia arteriovenous fistula and arrhythmia with

(8) J Mt S H p 19 303 309 M y J 195

slow to consider that the patient has cardiac disease As yet there is no adequate substitute for the careful history and the thorough physical examination in the decision as to the presence or absence of disorders of the heart.—Ed]

Studies Utilizing the Portable Electromagnetic Ballistocardiograph II Ballistocardiogram as Means of Determining Nicotine Sensitivity Nicotine affects the cardiodynamics in some individuals by causing tachycardia increased blood pressure and ECG changes There may also be definite changes in the ballistocardiograms Harry Mandelbaum and Robert A Mandelbaum[6] (Jewish Hosp Brooklyn) found three characteristic patterns (1) increased velocity of ventricular ejection causing larger ballistic amplitude (hyperkemia) (2) abnormal variation of the ballistic pattern with respiration and (3) presence of diminished HIJ and deep K pattern These changes were pronounced in patients with hypertension coronary artery disease and neurocirculatory asthenia but were also found in some persons with no heart disease

Patterns 2 and 3 are considered more serious indications than pattern 1 The hyperkemic response was found frequently in individuals without heart disease and was not considered evidence of harmful nicotine effect unless there was an associated abnormal ballistic pattern These changes were considered objective evidence of failure to adapt to the cardiovascular effects of nicotine and should guide the physician in the question of interdiction of tobacco Several patients who had positive results in smoking tests showed definite improvement in the ballistic pattern after abstention from tobacco

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CONGESTIVE HEART FAILURE

Comparison of Working and Nonworking Cardiac Patients is presented by Leonard J Goldwater Lewis H Bronstein and Beatrice Kresky[7] (Bellevue Hosp) to supplement an earlier report Functional results in 469 cardiac patients who continued in some form of useful employment after diagnosis of heart disease are compared with those in 111 who stopped work entirely Correlation of results indicated that the younger patients tended to continue to work whereas those over 55 at time of diagnosis tended to stop work Also those who had

(6) Circulat 5 885 891 Jun 1952
(7) A M A Arch Ind st Hyg 5 485 489 May 1952

normal in patients with coronary sclerosis quinidine intoxica tion perhaps with rheumatic heart disease and rarely in con genital heart disease acute glomerulonephritis and isolated myocarditis Noncoronary paroxysmal ventricular tachycardia as defined by the authors is ventricular tachycardia not ini tiated by acute myocardial infarction or digitalis poisoning it is not known to be followed by lethal ventricular fibrillation but if uncorrected may cause congestive heart failure When quinidine and procaine amide both often effective in restoring normal sinu rhythm are unavailing the authors recommend intravenous administration of lanatoside C which is safe and effective

Three cases are presented in which lanatoside C used intra venously on six occasions following concurrent with or in the absence of other measures was generally efficacious in restoration of normal sinus rhythm In one patient this digi talis preparation (as well as procaine amide papaverine and atropine) failed to restore normal sinus rhythm which finally responded to massive doses of quinidine by mouth but the lanatoside C was significantly innocuous

Clinical Study of Gitalin a water soluble amorphous mix ture of glycosides derived from Digitalis purpurea is presented by Milton K Hejtmancik and George R Herrmann[1] (Univ of Texas) The preparation was used for initial digitalization of 49 patients with cardiac decompensation and maintenance dosage was determined for 131 The average digitalizing dose was 6 5 mg (range 4 5 9 mg) and most patients were ade quately maintained on 0 5 mg daily The pharmacologic actions of gitalin are similar to those of digitalis leaf The manifesta tions of toxicity were similar in type to those noted with other preparations For 22 patients the average minimal maintenance dose was 0 54 mg and the average minimal toxic dose 0 91 mg a therapeutic index of 59 5% This therapeutic range is related to the degree of cardiac efficiency being much smaller in the patient with serious myocardial damage

Twelve patients who had previously failed to improve on well regulated digitalis therapy were treated with gitalin There was evidence of improvement in nine The other three did no better with gitalin than with other digitalis preparations

Gitalin may be the agent of choice for patients with con

(1) A M A Arch Int Med 90 4 33 August 1952

tachycardia may also be overlooked as possible causes that precipitate or aggravate congestive failure early detection and effectual treatment are often lifesaving Rheumatic fever although a fairly common factor in obstinate congestive failure is not readily remediable ACTH and cortisone may help to control the course of the disease thereby permitting more satisfactory treatment of the failing heart Bacterial endocarditis sometimes the cause of heart failure and its refractoriness may sometimes be eradicated before irreversible anatomic lesions perpetuate decompensation Pulmonary embolism is one of the more common causes of congestive failure and its refractoriness Hypertension may sometimes be relieved by sympathectomy or sodium restriction or cured by excising a pheochromocytoma Diet therapy may modify the course of congestive failure in hepatic cirrhosis The symptoms of digitalis intoxication may simulate those of intractable failure or vomiting caused by such intoxication may disturb electrolyte equilibrium thereby impairing response to digitalis Sufficient and proper use of sodium restriction mercurial and ammonium diuretics and watchful management of electrolyte equilibrium will often promote recovery from apparently unmanageable congestive heart failure

3 Is the form of cardiac disease amenable to surgery? Corrective surgery may be considered for constrictive carditis mitral stenosis and such congenital lesions as patent ductus arteriosus aortic coarctation pulmonic stenosis and septal defects

4 Is bed rest being properly advised and utilized?

5 Has improper or exaggerated treatment caused therapeutic unresponsiveness?

In practice systematic point by point survey of all contributing factors would eliminate much of the error in myocardial insufficiency which has become refractory to all of the known treatments

Usefulness of Intravenous Lanatoside C in Paroxysmal Ventricular Tachycardia Not Due to Myocardial Infarction is discussed by Edward Shapiro Herman Weiner and Jacob L Bernstein[9] (Los Angeles) Paroxysms of ventricular tachycardia occur in myocardial infarction and in digitalis intoxication but also not uncommonly are found in hearts which are

(9) Permanent Found M Bull 10 7 38 August 1952

Use of Digitalis in Infants and Children Clinical Study of Patients in Congestive Heart Failure Alexander S Nadas Abraham M Rudolph and John D L Reinhold[3] (Harvard Med School) discuss the management of 41 patients with congestive heart failure all of whom had signs of right sided failure (tachycardia tachypnea jugular vein distention and hepatomegaly) Left sided failure with pulmonary congestion was present in at least half the patient Peripheral edema was seldom present Response to digitalis was judged by disappearance of congestion Weight loss is not a reliable criterion in children The total digitalizing dose was usually administered within 24 36 hours in three or four divided doses after an observation period of at least 48 hours when feasible For initial digitalization most patients received digitoxin intravenously or orally lanatoside C intravenously was used in a few emergency cases For maintenance digitoxin was used exclusively

Cyanotic congenital heart disease was present in 17 non cyanotic congenital heart disease in 10 paroxysmal auricular tachycardia in 3 and rheumatic heart disease in 2 9 were considered to have primary myocardial disease indicating subendocardial sclerosis or isolated myocarditis

Patients with primary myocardial disease paroxysmal auricular tachycardia and rheumatic heart disease responded well Therapeutic failures were common in children with congenital heart disease especially those with cyanosis

There was no single ECG change that tended to appear any earlier than others as digitalization progressed The most frequent alteration was a shortening of the Q T_c ($Q\ T/\sqrt{\text{cycle length}}$) and this was quantitatively unrelated to the disease or the dose of digitalis In only four patients were ECG changes not evident by the third day of treatment and three of these never showed a clinical response to the drug

The effective digitalizing dose was correlated with age and clinical response of the patient but not with type of disease Children aged 2 or older who responded well to digitalis did so with doses of 0 01 0 02 mg /lb body weight most infants under age 2 who showed a satisfactory response required 0 02 0 03 mg /lb The maintenance dose was one tenth the digitalizing dose There was ECG evidence of toxicity in 11

(3) N w E gl d J Med 248 98 105 J 15 1953

gestive failure who do not maintain response to ordinary treatment

[A number of different investigators have now reported that gitalin has a more favorable toxic/therapeutic ratio than other digitalis preparations It should be noted that the dose of gitalin is considerably larger than that of the other purified preparations Both the initial dose and the maintenance dose are approximately five times as great However this does not constitute a disadvantage —Ed]

Studies with Intravenous Gitalin I Clinical and Electrocardiographic Observations Olga M Haring and Aldo A Luisada[2] (Mount Sinai Hosp Chicago) report on the use of gitalin intravenously in 16 ambulatory cardiac patients with congestive failure and in 4 normal subjects and compare its effects with those of strophanthin K lanatoside C and digitoxin An initial dose of 2 5 3 mg of gitalin was used in most instances and the total digitalizing dosage approached by diurnal intravenous injections was 5 0 mg There were no ectopic rhythms or drug intolerance This fact confirms previous reports that the therapeutic ratio of gitalin is higher than that of other glycosides

The changes in the heart rate with gitalin were similar to those caused by other digitalis glycosides and were particularly apparent 24 hours after full digitalization The ECG s failed to show any significant differences between gitalin and the other glycosides

The persistence of the S T and T changes was studied to evaluate the rate of elimination of digitalis derivatives from the body The T wave returned to normal within 24 hours after strophanthin administration 3-4 days after gitalin 4 5 days after lanatoside C and 5 7 days after digitoxin A successful intravenous maintenance therapy can be attained only if injections are given at intervals of 72 96 hours

Gitalin a derivative of Digitalis purpurea proved to be a powerful and safe digitalis preparation and is as effective by intravenous injection as by mouth Intravenously it can either be given semiweekly in doses of 2 5 mg or be used for rapid initiation of therapy after which digitalization can be continued by the oral route Gitalin appears to be the drug of choice for patients with congestive failure due to rheumatic carditis or coronary heart disease and for patients with congestive failure with ectopic rhythms

(2) Am Heart J 45 108 120 January 1953

ectopic tachycardia The data were considered insufficient to evaluate distinctive responses to the glucosides tested Likewise the authors *feel that further parenteral experimentation* including intramuscular injection will be necessary before the mechanism is ascertained

Experiments on cats showed that vomiting may occur *10 hours or longer* after *oral dosage* without any evidence of systemic digitalis action as determined by titration In man also delayed gastrointestinal reactions to digitalis may be the result not necessarily of a systemic action but rather of prolonged absorption with cumulative irritant stimuli in the gastrointestinal tract The authors do not propose substituting parenteral for oral administration of digitalis glucosides but *suggest that the use of the oral route alone may curtail the* therapeutic potentialities of these drugs and that supplementing oral with intravenous doses may enhance the cardiac action by by passing gastrointestinal toxicity

Mercurial Fastness in Patients with Congestive Heart Failure Correction of This State by Addition of Pyridoxine Effectiveness of mercurials in production of diuresis is limited by *the tendency of some patients to become resistant to them* Various combinations of such drugs as ammonium chloride ammonium nitrate sodium dehydrocholate ascorbic acid and aminophylline with a mercury compound have been successful *in re establishing diuresis* It has also been *found helpful* to change the particular mercury compound used if this is done before mercurial fastness has occurred Samuel Waldman *and Louis Pelner*[5] *(Brooklyn) suggest as an additional* method concomitant use of 100 *mg* pyridoxine with 2 cc of the mercurial compound given intravenously or intramuscularly Such a combination was used in *10* patients after resistance had developed to mercurial compounds *previously* used with or without concurrent ascorbic acid ammonium chloride etc Each patient was treated with mercuhydrine combined with *pyridoxine and prompt diuresis occurred* amounting to a 6 lb weight loss in the first 24 hours in two patients Resistance developed to this combination in one patient but was overcome by *return to previous* mercury combinations

The mechanism of pyridoxine action in enhancing mer

(5) Am J M S 5 34 45 J y 1953

patients but it was not of serious consequence it was not correlated with the size of the digitalizing dose but occurred *predominantly in those with primary myocardial disease* The patients with myocardial disease who responded best were those who had toxicity on low dosage The authors therefore regard toxicity and therapeutic effectiveness as evidences of sensitivity to digitalis

Difference in Relation of Cardiac to Emetic Actions in Oral and Parenteral Digitalization Harry Gold Theodore Greiner McKeen Cattell Walter Modell Joseph Gluck Raymond Marsh Sydney Mathes Dean Hudson Donald Robertson Leon Warshaw Harold Otto Nathaniel Kwit and Milton Kramer[4] (Cornell Univ) questioned whether the emetic effect of the digitalis glucosides in man is the result of a systemic action *as generally believed or the result of cumulative stimuli* from the gastrointestinal system The therapeutic implication is that the cardiac usefulness of the drugs may be blocked by gastrointestinal reactions which can be obviated by parenteral administration

Ten cardiac patients were given digitalis preparations *by both routes Each first received the drug orally* slowly until vomiting was induced the cardiac action of the drug was evaluated to that point The drug was then discontinued until there was partial or complete loss of effect after which parenteral doses were administered until the degree of cardiac action was *the same as or greater than that with the oral dose* or until vomiting occurred Four criteria were used for cardiac evaluation change in the RT T segment effect on the P R interval slowing of the apex rate in auricular fibrillation and abolition of auricular ectopic tachycardia Digitoxin digoxin lanatoside C and *digifolin** were used *Administration parenterally* was *generally* by the intravenous route

The degree of cardiac action at the threshold of gastrointestinal toxicity after oral dosage was reproduced by parenteral administration without gastrointestinal toxicity furthermore more cardiac action without vomiting was *possible* by the *parenteral method* In one patient this difference was *sufficient* to make a success of what would have been a therapeutic failure with digitalis orally since gastrointestinal toxicity occurred repeatedly just before abolition of an auricular

(4) Am J M d 13 124 144 Augu t 195

filtrate into acid urine are fundamental to preserving normal blood pH and conserving sodium Carbonic anhydrase is thought to catalyze the hydration of carbon dioxide to carbonic acid in the tubules thereby furnishing intracellular hydrogen ions which diffuse into the tubular lumen in exchange for sodium ions which are thereby conserved by the tubule cells The hydrogen ions combine with bicarbonate ions in the lumen to form carbonic acid which breaks down to provide carbon dioxide This diffuses freely across the tubular membrane and into the tubular cells The net result is reabsorption of sodium and bicarbonate and addition of hydrogen ions into the tubular lumen

Inhibition of carbonic anhydrase blocks this reaction and thereby accelerates the excretion of sodium and bicarbonate One inhibitor 6063 was studied by the authors in a group of 15 patients 3 of them had no cardiovascular or renal disease and served as controls and the other 12 were in congestive heart failure All but one of the cardiac patients were judged to be free from edema

METHODS—Two of the control and four cardiac patients had been on a diet containing 5 7 Gm sodium/day before the experiment the rest were on diets restricted to 0 2 0 5 Gm sodium/day for at least three days before the experiment All subjects were hydrated during the experiment After a period of control observation 750 mg of 6063 in 250 cc of 5% dextrose in water was given intravenously in 20 minutes Blood chemical studies were made by standard methods the bicarbonate content was calculated by the Henderson Hasselbalch equation with pH=6 10 for both blood and urine

In every patient urine output increased and there was consistent loss of weight from 0 5 to 2 7 Kg within 24 hours of taking the drug The urine invariably became alkaline in 30 minutes and stayed alkaline throughout the six hour experiment Bicarbonate excretion increased notably blood bicarbonate and pH levels showed a slight asymptomatic tendency to acidosis Sodium and potassium excretion increased in both quantity and concentration but were in no constant relationship with each other Sodium excretion greatly increased in patients with higher sodium content in the diet and was unrelated to differences in degree or type of heart failure Chloride excretion increased in quantity but decreased in concentration the absolute increase in chloride excretion appeared to be related to increased urinary flow Excretion of

curial diuresis is unknown—it may be at an enzymatic level The compound may be combined with mercurial diuretics as an additional recourse when the patient in chronic congestive heart failure becomes resistant to mercury

Hypochloremic Alkalosis Induced by Mercurial Diuretics in Congestive Heart Failure A Reversible Form of So called Refractory Heart Failure is reported by John F Stapleton and W Proctor Harvey[6] (Georgetown Univ) Refractoriness to mercurial diuretics often causes an unmanageable downhill course in congestive heart failure this is partly due to disturbed electrolyte balance One of the patterns of disturbance the low salt syndrome is well recognized another clinically similar but basically different disturbance is hypochloremic alkalosis presumably due to preferential excretion of the chloride ion in excess of sodium Whereas the typical pattern of the low salt syndrome consists of low serum sodium low chloride normal to low CO_2 and normal to elevated blood urea values in hypochloremic alkalosis the serum sodium level is normal but the chloride concentration is low the CO_2 combining power normal to elevated and the blood urea nitrogen content generally normal Diagnosis is differentiated in the laboratory as clinical symptoms (thirst anorexia nausea weakness apathy oliguria mental aberration) overlap and are common to both

The two conditions are treated differently Hypertonic salt solution is indicated for the low salt syndrome but ammonium chloride (6-8 Gm by mouth or 4 8 Gm in 1% solution administered slowly by vein) is used for hypochloremic alkalosis Well diluted hydrochloric acid may be given by mouth When the electrolyte pattern is corrected refractoriness to the mercurial diuretics is generally lost and they can then be reinstituted until clinical improvement is noted

Effect of Intravenously Administered *6063*, the Carbonic Anhydrase Inhibitor, *2 Acetylamino 1,3 4 Thiadiazole 5 Sulfonamide*, on Fluid and Electrolytes in Normal Subjects and Patients with Congestive Heart Failure is discussed by Charles K Friedberg Mark Halpern and Robert Taymor[7] (Mount Sinai Hosp New York City) Tubular reabsorption of almost all filtered sodium and conversion of the alkaline glomerular

(6) A M A A h I t Med 90 4 5 434 O t be 195
(7) J Cl In t 31 1074 1081 D ml 195

filtrate into acid urine are fundamental to preserving normal blood pH and conserving sodium Carbonic anhydrase is thought to catalyze the hydration of carbon dioxide to carbonic acid in the tubules thereby furnishing intracellular hydrogen ions which diffuse into the tubular lumen in exchange for sodium ions which are thereby conserved by the tubule cells The hydrogen ions combine with bicarbonate ions in the lumen to form carbonic acid which breaks down to provide carbon dioxide This diffuses freely across the tubular membrane and into the tubular cells The net result is reabsorption of sodium and bicarbonate and addition of hydrogen ions into the tubular lumen

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(6) A M A A b I t M d 90 4 5 434 O t b 195
(7) J Cl Inv st 33 10 4 1083 D ml 195

and during both exercise and recovery in 10 Four patients in this group showed T wave changes during exercise only none during recovery only and six during both exercise and recovery Thirteen patients had an abnormal Q T/T Q ratio (above 2 2) 9 an abnormal corrected Q T interval (Q T) and 3 ventricular premature beats Of the 21 patients with arterio sclerotic or hypertensive heart disease 12 had abnormal S T depression only during recovery or during both recovery and exercise None showed S T depression during exercise only An abnormal Q T (i e failure to shorten during recovery) was seen in 10 of the patients In the miscellaneous group one patient showed abnormal S T depression and another high T waves only during exercise A third patient had S T depression and diaphasic T waves only during early recovery No normal subject showed S T depression in excess of 1 mm a Q T/T Q ratio greater than 2 2 or ventricular premature beats

This study demonstrates that many of the significant ECG changes occurring during exercise are so evanescent that false negative ECG s may be obtained in about 20% of the patients with angina pectoris if tracings are made only after exercise

Electrocardiographic Exercise Test. The clinical utility of the ECG exercise test has been hampered by lack of a stand ardized procedure unfamiliarity with normal changes in the ECG following exercise and disagreement as to criteria for a positive result D Scherf and A I Schaffer[9] (New York Med College) review cardiac electrophysiology and the changes in the components of the ECG which occur in the normal and abnormal myocardium after exercise In particular deviations of the S T segment are evaluated

After exercise the S T vector tends to be oppositely directed to the QRS vector The ventricular gradient normally is directed approximately parallel to the QRS vector Tachy cardia tends to decrease the gradient evidenced by depression of the S T segment or lowering of the T waves in those leads which display an upright QRS complex A factor found in the tachycardia of exercise and not in that elicited by other means which may be termed the effort factor tends to increase the gradient Still another result of tachycardia apart from the gradient effect is accentuation of the S T segment and

(9) Am H rt J 43 9 2 946 J 1952

phosphates was increased to about the same degree as chloride

Compared to the effect of 2 cc mercuhydrin® intravenously 750 mg of 6063 intravenously caused considerably less increase in sodium and chloride excretion and did not promote as great a diuresis it did increase bicarbonate excretion far more than the mercurial diuretic

No significant effects on sodium potassium chloride phosphate or creatinine concentrations in the plasma were noted and no toxic effects observed

Despite the acidosis ammonia excretion was greatly diminished This supports the concept that the pH of the urine is more important in stimulating excretion of ammonia than the pH of the blood

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ELECTROCARDIOGRAPHY AND ARRHYTHMIAS

Studies of Electrocardiographic Changes during Exercise (Modified Double Two Step Test) were carried out by Paul N G Yu and Alfred Soffer[8] (Rochester N Y) on 38 normal subjects and 54 patients aged 18 69 with various cardiovascular diseases The latter included 21 with a history of angina pectoris 21 with arteriosclerotic and hypertensive heart diseases without a history of angina and 12 with miscellaneous diseases (rheumatic heart disease congenital heart disease intermittent claudication atypical chest pain and abnormal ballistocardiogram) An exploring precordial electrode was placed over the fifth intercostal space along the left midclavicular line or slightly to the left and an indifferent electrode over the right scapula The two step test was the same as that described by Master and associates except for the following modifications the CB_4 or CB_5 lead was used throughout the test and no tracings from limb leads were made a double two step test lasting three minutes was done on every subject unless interrupted by symptoms or definite ECG abnormalities and tracings were made before during and 30 90 150 seconds and 8 minutes after exercise or later

Abnormal S T depression considered by the authors to be 1 mm or more occurred only during exercise in 5 of the 21 patients with angina pectoris only during recovery in 2

(8) C I t 6 183 19 A g t 1952

the procedure should be carried out it does not seem justifiable to base the diagnosis of coronary artery disease mainly on these procedures The patient s hi tory the ob ervation of the effect of exercise and of other precipitating factors in inducing the pain and the ob ervation of the response of the pain to nitroglycerin or to other therapeutic measures still constitute the most valuable method of recognition of angina pec toris Attempts to adopt rule of thumb shortcuts are u ually disappointing —Ed]

Electrocardiogram in Mitral Stenosis J R Trounce[1] (Guy s Hosp) analyzed ECG changes in 75 cases of mitral stenosis in 35 of which cardiac catheterization was done The patients were candidates for mitral valvulotomy and no one was included who had clinical or radiologic evidence of predominant mitral regurgitation or aortic disease Diagnosis was based on physical findings and confirmed by fluoroscopy

Of 52 patients without auricular fibrillation 40% had P waves greater than 1 1 mm in lead I 22% had P waves greater than 2 5 mm in lead II and 72% had diphasic P waves in lead VI Duration of P waves in lead II exceeded 0 11 second for 48% Sixty one per cent had flat topped P waves in lead I or II 11% had pointed P waves and 31% had notchings gener ally associated with a flat topped P wave No correlation was found between amplitude breadth or area of P waves in lead I or II and the pulmonary artery pressure in the patients who had cardiac catheterization

Right axis deviation was considered present if in lead I S waves were equal to or greater than twice R waves and in lead III R waves were equal to or greater than twice S waves The converse indicated left axis deviation Of the 75 patients 29% had right axis deviation 70% had no axis deviation and 1% had left axis deviation Vertical heart position was evident in 68% All patients with right axis deviation and 29 without had an rRR pattern in the standard leads (small r in lead I and normal or large R in leads II and III) Of the 35 patients catheterized so that presence of the atrial septal defect could be excluded only 2 showed an RR pattern in lead V_1 never in lead V This would serve as a further useful point in differentiating mitral stenosis from atrial septal defect

Right ventricular hypertrophy was indicated in the ECG s of 35 patients (47%) and a further 34 had fluoroscopic evidence of right ventricular enlargement A high pulmonary

(1) B t H t J 14 185 19 Ap 1 19

T wave Posture too may affect the gradient When a patient with coronary artery disease performs exercise the ST T complex is influenced by the normal tendencies mentioned and in addition by inner layer ischemia tending to decrease the gradient The crucial function of the examiner in the exer cise test is to recognize which S T depression is due only to the decreased gradient of tachycardia and is therefore normal and which is due to ischemia and abnormal

The authors prefer a test in which a positive result is practically pathognomonic of coronary artery disease and *which includes a minimum of false positives* as opposed to a test designed to eliminate the possibility of coronary artery *disease which will have less rigid requirements for positivity* and will necessarily include some false positives They find *that the maximal normal S T depression after moderate exer* cise is 2 mm a value not accepted by all investigators some of whom consider a change of more than 0 5 mm abnormal The amount and type of exercise used are based on the patient s history and are chosen to require performance of exertion approximating that which will bring on symptoms but not exceeding the amount which the patient permits himself to perform daily There is no strict parallelism between the degree of ECG change and the patient s discomfort and thus chest pain is not a necessary or desirable feature of the test Tracings are taken immediately before immediately after and 2 5 and 10 minutes after exercise The first test is always limited to the amount of work which the patient does during his daily routine and if negative is an indication for subse quent tests with cautiously increased exercise

The ECG exercise test is most useful in patients with an atypical history negative clinical and ECG findings and *doubtful outcome of the therapeutic nitroglycerin test It is* not done on all patients with coronary artery disease Positive results are in the range of 80% comparing favorably with the results of other investigators

[Recently there has been a tendency to place increasing reliance on minor ECG changes following standardized exercise as an index to the diagnosis of coronary disease It should be noted that the authors of this article consider S T depression of less than 2 mm to be not significant while the authors of the preceding article consider a change of 1 mm or more to be significant These findings are in contrast to the publications of othe s who believe that a depression of 0 5 mm or more is s gnif cant In view of these discrepancies and the differences in opinion as to how

aVR and V_1 may be partially the extreme clockwise rotation of the heart but other factors must contribute.

The ECG s of normal children have features which in some ways resemble the patterns of right ventricular hypertrophy and may be differentiated by the aforementioned criteria

Nature and Treatment of Auricular Arrhythmias Myron Prinzmetal[3] (Univ of California at Los Angeles) proposes a unitary genesis for auricular premature systoles auricular paroxysmal tachycardia auricular flutter and auricular fibrillation in which a single ectopic focus in the auricles discharging at increasing frequency produces each of the auricular arrhythmias in the order listed

Studies on experimental animals utilizing high speed motion pictures (2 000 frames/second) and the cathode ray oscillograph have shown visually that a single auricular ectopic focus responding to electrical mechanical or chemical (aconitine) stimulation discharges impulses which spread radially at equal velocities Auricular fibrillation is characterized by minute irregular contractions continuously present and large rhythmic wavelike contractions The minute contractions invisible to the unaided eye and represented on the ECG by tiny rough irregularities in the F waves occur constantly throughout the auricular musculature and involve an area of auricular wall approximately 0 03 3 mm in diameter Superimposed on these are large more vigorous contractions sweeping across the auricle at 400-600/minute probably manifest in the ECG as F waves This can be induced in the experimental animal by stimuli applied at the rate of about 400/minute termed the fibrillation threshold

Auricular flutter was produced when stimuli were applied to the auricle at the rate of 300-400/minute The flutter waves were similar to the large waves of auricular fibrillation the tiny irregular contractions did not occur Various procedures were done to test the presence of a circus mechanism in this disorder The path of the hypothetical circus motion was interrupted Paired electrodes were placed in various locations in relation to the discharging focus All the evidence by motion picture oscillography and failure to abolish the arrhythmia by mechanical interruption of a postulated circus

(3) Canad M A J 66 535 540 J 195

artery pressure was usually associated with ECG evidence of right ventricular hypertrophy although right ventricular hypertrophy was present in some patients with apparently normal pulmonary artery pressure Some correlation could be demonstrated between ECG evidence of right ventricular hypertrophy and pulmonary artery pressure

Electrocardiogram in Normal Children and in Children with Right Ventricular Hypertrophy The need for accurate diagnosis in congenital heart disease has greatly increased the importance of the various ECG patterns found in right ventricular hypertrophy This is particularly important in children in whom the normal patterns may closely simulate those of right ventricular hypertrophy J F Goodwin (Univ of Sheffield) compared the ECG patterns of 53 healthy children aged 16 months to 15 years and those of 36 children aged 3 14 with congenital heart disease and clinical and radiologic evidence of right ventricular hypertrophy In 72% cardiac catheterization or angiocardiography showed increased right ventricular pressure or right ventricular enlargement respectively and in the three patients on whom autopsy was done right ventricular hypertrophy was found The particular points studied were the pattern of the ventricular complex and the ventricular activation time in leads aVR V_1 and V_5 the Q/R or R/S ratios in lead aVR and the R/S ratio in leads V_1 and V_5 the R/S ratio in lead V_5 divided by the R/S ratio in lead V_1 the direction of the precordial T waves and the position of the heart

Results of this study suggest that the important signs of right ventricular hypertrophy are a R/S ratio of greater than 1 with ventricular activation time greater than 0 03 second in lead V_1 and a Q/R ratio of less than 1 in lead aVR Patients with right ventricular hypertrophy may show either or both of these signs but in none were both patterns absent

Inversion of the precordial T waves in leads V_1 to V_3 was often found in normal children and was of no value in the diagnosis of right ventricular hypertrophy Conversely in the same leads the T wave was often upright in patients with right ventricular hypertrophy

The mechanism of the Q/R ratio of less than 1 in leads

(2) B t H t J 14 173 184 Ap 1 195

there were no instances of the syndrome The syndrome may be missed if there is strict adherence to the figure of 0 10 second or greater as indication of prolongation of the QRS time Duration of the QRS complex in infants (0 04-0 05 second) is normally shorter than in the older child or adult and may be prolonged when it measures 0 08 or 0 09 second

Occurrence of paroxysms of tachycardia generally is the clue to diagnosis These are accompanied by vomiting irrita bility ashen gray color and prostration Cardiac failure with its characteristic signs may supervene Tachypnea and dysp nea occur

Engle recommends 0 35 mg digitalis/kg body weight or 0 035 mg digitoxin/kg in divided doses over 12 24 hours as a proper digitalizing dose The daily maintenance dose is 10 20% of the total digitalizing dose Quinidine sulfate fre quently terminates an attack but the optimal dosage schedule for infants has not been determined In an emergency 1 mg acetylcholine bromide may be given intravenously doubled every 10 15 minutes until conversion is accomplished If acetylcholine is used atropine should be available in a syringe if needed as an antidote Other suggested drugs are procaine amide hydrochloride neostigmine methylsulfate and phenyl ephrine neo synephrine* hydrochloride Paroxysms often can be stopped by supraorbital or carotid sinus pressure or—when the child can co operate—by gagging vomiting breath holding or assumption of a particular position

[Paroxysmal tachycardia in infants is likely to be a more serious dis ease than in olde children or in adults The ventricular rate may be ex cessively fast—up to 300/minute or more Response to the usual drugs such as digitalis and qu n dine i often d sappo nting Neostigmine which the author ment ons i sometimes a life saving drug —Ed]

Neostigmine Bromide Orally in Prevention of Paroxysmal Supraventricular Tachycardia Eugene B Levine and Gene Blumfield (College of Med Evangelists) found that neostig mine bromide a relatively nontoxic drug effectively prevented paroxysmal supraventricular tachycardias in 6 of 20 patients when given in oral doses to tolerance ranging from 3 75 mg twice daily to 30 mg four times a day None of eight patients with rheumatic heart disease responded to the treatment but eight who had no demonstrable organic heart disease had particularly good results It apparently is not as effective as

(5) A n. West M d & S g 6 642 647 Octobe 1952

path further established the concept of a single ectopic focus discharging radially directed waves of equal velocity

Auricular tachycardia differed in at least three respects from auricular flutter (1) the rate of discharge from the ectopic focus was slower (2) each wave was followed by ventricular response—no A V block existed and (3) the propagation of the individual tachycardia wave was faster than the flutter wave

When aconitine is applied locally to the auricle fibrillation usually results in a few minutes If the ectopic focus is cooled by spraying with ethyl chloride the rhythm often changes systemically from fibrillation to flutter to tachycardia and finally to sinus rhythm with auricular premature systoles An orderly progression in the reverse direction may be seen as the cooling effect wears off Motion pictures of these experiments show the contraction waves to be similar except for the rate and speed of conduction

[The evidence cited by the author for the unitary genesis of the auricular arrhythmias appears to be very strong It is not yet universally accepted as many investigators still adhere to the concept of the circus movement as an explanation for auricular fibrillation and for auricular flutter There is one clinical observation which lends strong support to Prinzmetal s concept This is the occasional finding in a single patient of all of the auricular arrhythmias within a few minutes Thus a patient may have premature auricular beats arising from varying foci short runs of paroxysmal tachycardia auricular flutter and auricular fibrillation all alternating with each other within a period of a few minutes It is difficult to account for such observations on the assumption that an ectopic focu i responsible for auricular premature beats and for auricular tachycardia on the one hand while a circus movement is responsible for auricular flutter and auricular fibrillation on the other hand —Ed]

Wolff Parkinson White Syndrome in Infants and Children Mary Allen Engle[4] (Cornell Univ) reports on four infants and children with the Wolff Parkinson White syndrome and reviews the 29 cases reported in the literature One of the author s patients was 6 days old when the pre excitation phenomenon was found on ECG symptoms compatible with tachycardia had dated from the first day of life—findings which suggest that the condition is congenital Rarity of the disorder is borne out by the review of several series of articles on ECG s in childhood in which incidence is 0 04% in 5 600 children in another series of 550 children two cases occurred and in a composite group of 3 400 normal infants and children

(4) A M A Am J D Child 84 69 705 D mbe 195

there were no instances of the syndrome The syndrome may be missed if there is strict adherence to the figure of 0 10 second or greater as indication of prolongation of the QRS time Duration of the QRS complex in infants (0 04-0 05 second) is normally shorter than in the older child or adult and may be prolonged when it measures 0 08 or 0 09 second

Occurrence of paroxysms of tachycardia generally is the clue to diagnosis These are accompanied by vomiting irrita bility ashen gray color and prostration Cardiac failure with its characteristic signs may supervene Tachypnea and dysp nea occur

Engle recommends 0 35 mg digitalis/kg body weight or 0 035 mg digitoxin/kg in divided doses over 12 24 hours as a proper digitalizing dose The daily maintenance dose is 10 20% of the total digitalizing dose Quinidine sulfate fre quently terminates an attack but the optimal dosage schedule for infants has not been determined In an emergency 1 mg acetylcholine bromide may be given intravenously doubled every 10 15 minutes until conversion is accomplished If acetylcholine is used atropine should be available in a syringe if needed as an antidote Other suggested drugs are procaine amide hydrochloride neostigmine methylsulfate and phenyl ephrine neo synephrine® hydrochloride Paroxysms often can be stopped by supraorbital or carotid sinus pressure or—when the child can co operate—by gagging vomiting breath holding or assumption of a particular position

[Paroxysmal tachycardia in infants is likely to be a more serious di ease than in older children or in adults The ventricular rate may be ex cessively fast—up to 300/minute or more R sponse to the usual drugs such as digital s and quinid ne is often d sappointing Neostigmine which the author mentions i sometimes a life saving drug —Ed]

Neostigmine Bromide Orally in Prevention of Paroxysmal Supraventricular Tachycardia Eugene B Levine and Gene Blumfield (College of Med Evangelists) found that neostig mine bromide a relatively nontoxic drug effectively prevented paroxysmal supraventricular tachycardias in 6 of 20 patients when given in oral doses to tolerance ranging from 3.75 mg twice daily to 30 mg four times a day None of eight patients with rheumatic heart disease responded to the treatment but eight who had no demonstrable organic heart disease had particularly good results It apparently is not as effective as

(5) A n. West M d & S g 6 64 647 O tobe 1952

quinidine but sometimes gives good results after quinidine and digitalis have failed or when they are not desirable This medication potent in many instances of paroxysmal supraventricular tachycardia is a valuable preparation when appropriately used

Simultaneous Independent Paroxysmal Tachycardias were encountered in seven patients by Lionel M Bernstein Luke R Pascale Armand Littmann and Edmund F Foley[6] (Cook County Hosp) Diagnosis was unequivocal in three patients with paroxysmal auricular tachycardia converting to a sinus rhythm without effect on the ventricular mechanisms demonstrable on ECG Diagnosis was inferential in four because auricular flutter was demonstrable immediately after and presumably during runs of ventricular tachycardia Paroxysmal ventricular tachycardia was diagnosed on the basis of gradual widening of QRS complexes and gradual slowing then suppression of paroxysms after intravenous administration of procaine amide hydrochloride Aberrant ventricular conduction of transmitted auricular impulses could not be definitely excluded

Except for one patient with rheumatic heart disease the double tachycardias were generally found in patients with advanced coronary disease All patients here had a history of cardiac decompensation before the onset of arrhythmias Procaine amide hydrochloride intravenously suppressed the paroxysmal ventricular pacemaker whenever it was used Within 72 hours of diagnosis four of the seven patients died One died after five months The recognition of two independent tachycardias is important in deciding what therapy should be used to slow the heart Final outcome is apparently determined by the severity of the underlying heart disease

Premature Ventricular Contractions and Exercise are discussed by Richard H Mann and Howard B Burchel[7] In 11 of 21 patients who had premature ventricular contractions after a modified Master exercise test ECG s taken before exercise had not demonstrated such arrhythmias Coronary insufficiency was diagnosed in the 11 on the basis of a 2 mm or greater depression of the RS T segment after exercise and the opinion of the cardiologist The other 10 patients had had

(6) J A M A 150 446 451 Oct 4 1952
(7) P oc Staff M t M yo Cl n 27 383 389 S pt 24 195

premature ventricular contractions before the exercise test Although frequency of premature contractions increased after exercise in seven only two patients had coronary insufficiency One patient with clinical coronary insufficiency could exercise only minimally the exercise test results were considered within normal limits despite evidence of coronary insufficiency by other criteria In one patient not included in the study premature ventricular contractions were abolished by exercise Coronary insufficiency was indicated both by clinical study and the exercise test Loss of premature contractions with exercise does not exclude coronary insufficiency

Although not diagnostic precipitation of ventricular tachycardia (or premature contractions) by exercise should suggest cardiac disease When premature ventricular contractions persist or become more frequent after exercise conclusions are difficult to draw The exercise test is functional although positive results are good evidence of coronary insufficiency negative results do not exclude the condition With this qualification it can be said that patients whose premature ventricular contractions persist or increase in frequency after exercise most often showed no evidence of coronary insufficiency

Origin and Essence of Morgagni Adams Stokes Syndrome The pre automatic pause of the heart during establishment of idioventricular rhythm in patients with recurring heart block has long been considered the chief cause of syncopal attacks However S de Boer[8] (Amsterdam) feels that this accounts for but a small fraction of attacks Others arise during periodic ventricular fibrillation or flutter in presence of complete heart block and in some individuals there is a rhythm known as periods of Luciani consisting of groups of systoles interspersed with longer pauses analogous to Cheyne Stokes respiration Syncopal attacks may also be caused by paroxysms of bradycardia a result of recurring second degree auriculoventricular block Sudden onset of bigeminy or multiple premature systoles without disturbance of conduction may so decrease the effective cardiac output that syncope occurs In a few patients the vagus effect on the heart is inordinately increased—by pressure inflammation or psychogenic stimulation—and paroxysmal syncope may result

Although restrictive anatomic or physiologic etiologies

(8) A I t M d 37 48 64 J ly 1952

have been described as delimiting Morgagni Adams Stokes seizures the author considers the terminology to include every disturbance of heart action that begins and ends abruptly causing such interruption of circulation that more or less complete cerebral ischemia results

Effectiveness of Nupercaine® Hydrochloride and Phenobarbital Sodium in Suppression of Ventricular Tachycardia Associated with Acute Myocardial Infarction was tested by Abdo Bisteni and A Sidney Harris[9] (Louisiana State Univ)

METHODS—Ventricular tachycardia was produced in dogs by gradual ligation of the anterior descending coronary artery occurring within 16 24 hours after operation in almost all animals Nupercaine® was given by slow intravenous injection 0 5 2 0 mg/kg diluted to 10 20 cc with Locke s solution or by continuous intravenous infusion of nupercaine® 1 2 mg/kg in 50 cc Locke s solution at the rate of 50 cc of fluid in 30 minutes A successful result was considered one in which the ectopic rate was reduced to zero and maintained at a level less than half the pretreatment control rate for four hours or longer

Intravenous administration of nupercaine® alone to 4 unanesthetized animals on the first day after occlusion and to 15 on the second day after occlusion produced ectopic impulse suppressor action in every case However in all four first day tests and some of the second day tests there were retching and vomiting Convulsions occurred in two of the first day tests

In five dogs nupercaine® intravenously was preceded by morphine 3 5 mg/kg given subcutaneously Four animals had satisfactory reduction of ectopic impulses but all had convulsions There was no vomiting

Nupercaine® was given to seven dogs following sedation with phenobarbital sodium 25-40 mg/kg Neither vomiting nor convulsions occurred and control of the arrhythmia was achieved in all The preferred dose was 25 mg/kg phenobarbital

Pentobarbital sodium 10 15 mg/kg, was given to four dogs and followed by the nupercaine® Arrhythmia control was excellent There was no vomiting or convulsions The duration of protection against toxic side reactions was not as great as with phenobarbital

Blood pressure tended to rise or remain constant in all slow administration tests In some rapid administration tests

(9) Circulation 7 523 53 April, 1953

periods of prolonged QRS deflections and hypotension occurred When the fast infusion was stopped all signs returned to normal within 30 seconds No fatalities occurred in any of the experimental dogs treated with nupercaine®

Rapid intravenous administration 8 mg/kg/hr in two dogs not operated on that had previous sedation with 15 mg pentobarbital/kg produced heart block and then cardiac arrest after 22 and 24 5 mg/kg respectively

Nupercaine® with phenobarbital is a relatively safe method for treatment of ventricular tachycardia and early carefully controlled clinical application is recommended

Transient Ventricular Fibrillation V Effects of Oral Administration of Quinidine Sulphate on Patients with Transient Ventricular Fibrillation during Established Atrioventricular Dissociation According to Sidney P Schwartz M Price Margolies and Anthony Firenze[1] (New York City) although quinidine sulphate reportedly helps to prevent or abolish episodes of transient ventricular fibrillation in patients with complete heart block substantiation of the reports is inadequate Three patients with recurrent transitory ventricular fibrillation were given quinidine orally according to one of three schedules 0 2 Gm hourly a single dose of 0 4 Gm and a single dose of 0 67 Gm The results of all tests were comparable despite variation in requisite dosage and intensity of response

1 The initial effect was on intraventricular conduction with early enlargement and negativity of T waves and prolongation of associated RS T segments Simultaneous development of premature beats arising from the ascending limbs of the T waves produced deformed ventricular complexes known to be forerunners of ventricular fibrillation

2 There was a progressive increase in the duration of the returning cycles which followed premature ventricular beats that appeared at the same time When complete heart block is present and the ventricular rhythm is disturbed by an extrasystole the length of the returning cycle is usually precisely that of the initial cycle Sometimes the returning cycle is shorter than the initial cycle The returning cycle has been found to increase in duration after cardiac fatigue but the increased duration is precipitated early by quinidine indicating increased refractoriness of heart muscle

(1) Am H rt J 45 404 415 M h 1953

3 Recovery from prolonged ventricular fibrillation is characterized by a protracted period of ventricular asystole succeeded by periodic standstill of the ventricles and atria when the fibrillary process is ended Quinidine also causes these changes to appear earlier than usual it prolongs the ventricular standstill immediately after fibrillation ceases and prevents the development of postfibrillary periods of tachysystole which usually follow the shorter periods of ventricular fibrillation

The authors feel that the drug was responsible for the development of recurrent periods of transient ventricular fibrillation that persisted for hours once the mechanism set in after its use

Quinidine sulphate is contraindicated in patients with transient ventricular fibrillation during established atrioventricular dissociation

[In the past uncertainty has existed concerning the possible value or harm of quinidine in patients of this type On the one hand the drug has been thought to be indicated because of its tendency to prevent ventricular fibrillation in some patients On the other hand quinidine has been thought to be contraindicated in patients with heart block because of the tendency to inhibit ectopic impulse formation upon which life may depend when auriculoventricular dissociation exists The study of Schwartz and his colleagues would appear to indicate that the disadvantage of using quinidine in the presence of grave impairment of conduction outweigh the theoretical advantage of the antifibrillatory effect.—Ed]

Action of Nor epinephrine Epinephrine and Isopropyl Nor epinephrine on Rhythmic Function of Heart in patients with induced cardiac standstill (hyperactive carotid sinus reflex) and with complete heart block has been studied by Morris H Nathanson and Harold Miller (Los Angeles) After intravenous injection of 0 02 mg isopropyl nor epinephrine (isuprel®) cardiac standstill could no longer be produced in patients with hyperactive cardioinhibitory carotid sinus reflex When compared with the action of epinephrine (0 03 mg intravenously) isuprel® showed the following differences it did not produce a pressor response was more potent and had no tendency (as observed with epinephrine) to abolish the standstill by stimulating lower ventricular foci Nor epinephrine was found to be without effect in abolishing induced cardiac standstill although it produced a considerable pressor response Both epinephrine and isuprel® caused a sustained increase in the ventricular rate of patients with heart

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block Nor epinephrine caused but a slight and very transient increase in ventricular rate Isuprel® given subcutaneously in doses of 0 2 mg caused definite and sustained increase in ventricular rate When it was given sublingually in doses of 15 and 30 mg the response was less but unequivocal duration was as long as two hours in some patients however as con trasted with the short (10 15 minutes) duration with intra venous administration

Nor epinephrine although causing little increase in ven tricular rate did produce excitation of lower ventricular foci resulting in multifocal ectopic beats Epinephrine had a similar tendency in the early phase of its action However isuprel® acted primarily on the basic pacemaker

In view of the observation that ventricular fibrillation is often present during the cardiac failure of the Morgagni Adams Stokes syndrome it seems advisable to use isuprel® in prevention and treatment of this condition because although effective in restoring rhythmicity it does not seem to pre dispose to lower ventricular arrhythmias as do nor epineph rine and epinephrine The authors suggest the sublingual use of isuprel 15 mg three or four times a day for prevention of the Morgagni Adams Stokes seizures

[This appears to be an important contribution The management of heart block with syncopal episodes is unsatisfactory in many patients If further study on additional subjects confirm the good results of isopropyl nor epinephrine in this disorder this drug will apparently become the treatment of choice —Ed]

RARE TYPES OF HEART DISEASE

Postpartum Myocardosis Robert M Woolford[3] (Univ of Cincinnati) reports five cases of congestive heart failure which developed soon after delivery These apparently fall into the category of postpartum myocardosis one of several terms applied to a disease characterized by fairly constant symptom atology and pathologic evidence of nonspecific degenerative changes in the myocardium unaccompanied by inflammation Typically there is congestive heart failure with dyspnea pul monary congestion and edema Two frequent signs are a diastolic gallop and an accentuated pulmonic second sound Hemoptysis may be present and many patients have serous

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effusion The blood pressure is increased Chest and upper abdominal pain is common Much of it is due to emboli but some of the descriptions in the literature are suggestive of coronary insufficiency The ECG is abnormal but the findings are inconstant and nonspecific Characteristically the disease occurs within a month post partum in a patient with no history of cardiac failure Response to treatment is poor but mortality figures vary widely Four of Woolford's five patients died

The cause of this condition is problematic Hypertension is usually present at least to a moderate degree and may be a contributory factor Cor pulmonale is suggested as a possibility in view of the frequency of pulmonary emboli and respiratory distress Also there is the factor of nutritional deficiency common during pregnancy In the author's series beriberi heart disease was considered but none of the patients improved with thiamine administration

In considering borderline cases Woolford reports a case in which a patient with long standing but well compensated heart disease went into congestive failure in the postpartum period As the load on the heart is considered to be maximum four to six weeks before delivery failure should occur then if it is due to the increased demands of pregnancy on an already damaged heart

Endocardial Fibroelastosis Forrest H Adams and Benjamin Katz[4] (Univ of Minnesota) review 21 cases in 4 of which only clinical diagnosis was made as the patients survived The major symptoms are generally related to left heart failure frequently accompanied by respiratory disease These include dyspnea cyanosis listlessness and vomiting Mitral or aortic murmurs may be heard The ECG usually shows evidence of pronounced left ventricular hypertrophy and changes compatible with strain and anoxemia—low negative or diphasic T waves depressed S T segments and normal or increased amplitude of the QRS complex The disease although usually of short duration before death may be protracted and the patients can be kept alive by use of supportive therapy and digitalis in some instances

Endocardial fibroelastosis can usually be differentiated from simple mitral or aortic lesions by the relative benignancy of the valve lesion It can be differentiated from myocarditis

(4) J P d t 41 241 552 A g t 195

by ECG results as well as the presence in myocarditis of elevation of the acute phase proteins

The authors do not consider the hypothesis that fibro elastosis is a collagen disease tenable Observations indicate that the disease can be diagnosed clinically in certain instances It must be added to the increasing list of possible causes of sudden death in infants

Anoxia as Cause of Endocardial Fibroelastosis in Infancy Many theories have been advanced regarding the genesis of endocardial fibroelastosis in infancy Frank R Johnson[5] (Northwestern Univ) made an anatomic and histologic study of 210 congenitally malformed hearts and compared them with two control groups—25 normal hearts from infants and hearts from adults exhibiting glycogen storage disease Fiedler s interstitial myocarditis and other diseases

Diffuse endocardial fibroelastosis was seen in 23 of the *congenitally malformed hearts* The congenital defects were anomalous left coronary arising from the pulmonary artery hypoplasia of the aorta congenital mitral stenosis congenital mitral and aortic stenosis idiopathic hypertrophy premature closure of the foramen ovale pulmonary or aortic atresia without interventricular septal defect and pulmonary and tricuspid atresia with small interventricular septal defect Anoxia is common to all these lesions It may be due to inadequacy of the circulation or the presence of unoxygenated blood during intrauterine life

A review of the literature showed 36 cases of aberrant left coronary artery arising from the pulmonary artery In these cases and five in the present series there was diffuse fibro elastosis of the single chamber which was the probable area of anoxia namely the left ventricle

If the foramen ovale closes prematurely before birth and mitral atresia is present the left atrium is bathed in unoxy genated blood The left ventricle may escape this fate if there is an interventricular septal defect Reports of premature closure of the foramen ovale an uncommon lesion show fibroelastosis of both chambers of the left heart except when closure is accompanied by an interventricular septal defect In one case with mitral atresia and an interventricular septal defect endocardial disease was present only in the left atrium

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in another with an interventricular defect but a patent mitral valve there was no fibroelastosis

Stagnation anoxia from valvular atresias may occur three hearts with pulmonary atresia showed diffuse fibroelastosis of the right ventricle wherein the blood presumably entered and became trapped One heart with pure aortic atresia had similar changes limited to the left ventricle

Mechanism and Incidence of Cardiovascular Changes in Paget's Disease (Osteitis Deformans) are discussed by C Franklin Sornberger and Magnus I Smedal[6] (Lahey Clinic) Cardiovascular disease is significantly increased in patients with extensive Paget s disease and is considered to be the leading cause of death It is a result of several factors There is increased vascularity of the affected portions of the skeleton which may in time reduce cardiac reserve In addition there is probably increased incidence and severity of arteriosclerosis which may be associated with hypertension Arteriosclerosis and calcareous deposits involving the aortic and mitral valves often appear in advanced disease

The numerous and severe deformities of the chest cage accompanied by respiratory distress may predispose to right heart failure through anatomic interference with pulmonary flow Increased incidence of cardiac enlargement is demonstrable in patients with extensive Paget s disease and is related to extent of bony involvement It is not demonstrable in patients with localized disease Patients with extensive osteitis deformans should be classified as having potential heart disease and should have periodic examinations

Nutritional Heart Failure is surveyed by G L Brinkman[7] (Christchurch N Z) Vitamin B_1 deficiency is the only avitaminosis currently recognized as productive of heart disease Among the anatomic changes are endocardial fibrosis as a prominent feature and hypertrophied myocardium occasionally with extensions of the endocardial fibrosis and hydropic degeneration Mural thrombi are often found in the areas of endocardial fibrosis and arrhythmias are common The structural change may be irreversible which explains why beriberi heart disease sometimes fails to respond to thiamine therapy Thiamine deficiency causes an abnormally high muscle concentration of lactic acid which leads to

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contraction of the blood vessels with resulting ischemia and fibrosis of the endocardium This in turn occludes the thebesian vessels and causes further myocardial ischemia thus establishing a vicious cycle Vitamin B_1 deficiency is also directly destructive to muscles since it interferes with pyruvic acid metabolism Two forms of beriberi heart disease are postulated the acute form due to gross vitamin deficiency associated with beriberi and responding to specific therapy and the subacute form due to subminimal avitaminosis with no neuritis but with irreversible cardiac damage

Another type of endocardial fibrosis associated with eosinophilia has been described in South Africa where it constitutes 10% of all myocardial failure The native diet is high in thiamine but extremely low in protein This is considered a nutritional heart failure of unknown etiology There are no histologic myocardial changes

The Bantu of South Africa on a grossly and generally deficient diet often have a type of heart failure which responds to a good varied diet but is refractory to vitamin B_1 There is no evidence of valvular or coronary disease in the hypertrophic heart but interfibrillary edema in the heart and liver damage including fatty infiltration portal cirrhosis and hemochromatosis No endocardial fibrosis or hydropic degeneration of the myocardium occurs

The author emphasizes that endocardial fibrosis regardless of etiology tends to be a self perpetuating lesion which continues inexorably to self destruction

PULMONARY CIRCULATION

Pulmonary Embolism is discussed by Louis Wolff[8] (Harvard Med School) Aseptic blood clots (bland emboli) may originate from the valves or chambers of the right heart and lodge in the pulmonary arterial tree but the great majority have their source in the large venous channels leading to the right heart most commonly in venous thrombi of the lower extremities The mechanism of intravascular coagulation of blood is poorly understood but it is of clinical importance that pulmonary emboli occur chiefly in bedridden patients

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generally over age 30 and that there is a high incidence in patients with heart disease

Lodgement of a clot in the pulmonary arterial tree produces many derangements of normal function (1) local disturbances in the pulmonary circulation (atelectasis infarction pleural effusion) (2) a sharp rise in right ventricular pressure and a drop in the left ventricular pressure (3) abnormal reflexes originating in the pulmonary vasculature the bronchi diaphragm coronary arteries neurogenic mechanism of the heart and in the peripheral vascular system and (4) anoxia The particular pathologic physiology of each case will depend on the interrelationship of these factors the caliber of the vessels occluded and the propagation of the emboli and the pre embolic state of the cardiovascular system

Chest pain is the most common single symptom occurring in 75% of cases It is of three types from local disturbance of the pulmonary circulation from pleuritis and from secondary impairment of the coronary circulation Anginal pain or the pain of myocardial infarction can generally be differentiated from the pulmonary artery pain of embolism by clinical and laboratory findings Fever leukocytosis and increased sedimentation rate are commonly present at the time clinical manifestations are first noted in pulmonary embolism but rarely within the first 24 hours after myocardial infarction In addition the ECG pattern of acute cor pulmonale is noted frequently—prominent S_1 prominent Q_3 inverted T_3 and normal QRS complex in the aVF lead which appear suddenly and rapidly return to normal Dyspnea is noted in almost half the patients Cough occasionally with hemoptysis is common

Sudden vascular collapse may be the first indication of a pulmonary embolus preceding by hours or days other manifestations The signs of acute cor pulmonale are prominent pulsations to the left of the sternum due to dilatation and overactivity of the pulmonary artery and conus dilatation and pulsation of the jugular veins cyanosis and at the pulmonic valve area marked accentuation of the second heart sound loud systolic murmur sounds resembling a pericardial friction rub and a pronounced protodiastolic gallop rhythm These signs appear suddenly but may be transient if peripheral vascular collapse or right heart failure supervenes

Fluoroscopy is more valuable than ordinary x ray for

it demonstrates the hyperactivity of the pulmonary system often an elevated and inactive leaf of the diaphragm as well as the areas of atelectasis or pulmonary avascularity The involved pulmonary artery segment may be surrounded by hazy infiltration due to edema in the acute phase this gradually subsides

In the diagnosis of acute pulmonary embolism it is important to recognize the variability as well as the multiplicity of symptoms and the fact that often the origin of embolization is not clinically demonstrable Embolism must be considered whenever patients who are candidates for the disease display unexplained vascular collapse unexplained syncope paroxysmal auricular fibrillation hemoptysis unexplained fever pulmonary edema cyanosis or jaundice

The treatment of pulmonary embolism and the efficacy of prophylactic measures are matters of debate Treatment by oxygen inhalation morphine atropine papaverine digitalis and maintenance of intravascular pressure are of help Vein ligation is indicated preoperatively for all patients who have or who are candidates for thromboembolism as well as in all situations where anticoagulants are otherwise contraindicated or ineffective Anticoagulants are used when surgery is not contemplated when the risk of vein ligation is great when vein ligation is ineffective and when they are not contraindicated by bleeding history or tendency

Chronic Massive Thrombosis of Pulmonary Arteries D R Keating J N Burkey H K Hellerstein and H Feil[9] (Western Reserve Univ) have observed this unusual disease in seven patients Pulmonary artery thrombosis may be (1) a direct involvement from intrinsic lung disease (as infection or tumor) or (2) a development of diffuse vascular disease of the lungs usually secondary to degenerative or chronic inflammatory disease or to mitral stenosis although it is occasionally the result of a primary vascular inflammatory process Here the following events occur pulmonary hypertension right ventricular hypertrophy right sided heart failure and thrombosis of the pulmonary artery aggravating the existing disease and resulting in sudden death

In the cases reported the coexisting diseases were pulmonary emphysema (generally of mild degree) adenocarcinoma of

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the stomach and chronic alcoholism with avitaminosis Patients with pulmonary emboli and those with primary cor pulmonale are most susceptible to pulmonary thrombosis The symptoms are often those of right sided heart failure cyanosis may be present and dyspnea is pronounced There is often ECG evidence of right axis deviation In one patient there was a change from left to right axis deviation within eight months

X ray examination may show diminished vessel markings in the parts of the lung fields supplied by the thrombotic arteries and if the patients survive long enough it may be possible to observe progressive enlargement of the hilar arteries There is significant lack of pulmonary congestion The diagnosis of chronic pulmonary artery thrombosis should be considered when right sided heart failure occurs without pulmonary congestion indicating that obstruction exists in the lesser circulation

Chronic Pulmonary Heart Disease Samuel Oram[1] (King's College Hosp London) reports that most cases of pulmonary heart disease result from chronic obstructive emphysema (from either infection or asthma) or are secondary to pulmonary fibrosis due to pneumoconiosis congenital pulmonary cystic disease or kyphoscoliosis This group has been termed anoxic pulmonary heart disease and the cardiac embarrassment is the result of although not quantitatively correlated with the emphysema A second smaller group the so called hypertensive pulmonary heart disease in which the primary disease is in the pulmonary arterial tree rather than the lung parenchyma includes primary pulmonary hypertension polyarteritis nodosa schistosomiasis amyloidosis sarcoidosis and scleroderma (when these affect the pulmonary arterioles) and the uncommon diseases of the pulmonary artery itself (aneurysm and obstruction of the artery or the right ventricular conus by aortic aneurysm) The differentiation of the two basic groups is important because they are treated quite differently

Anoxic pulmonary heart disease due to chronic obstructive emphysema manifests itself clinically by three groups of signs those resulting from the pulmonary disease itself those produced by right ventricular and pulmonary artery hypertrophy and those of right ventricular failure

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Signs of pulmonary fibrosis and emphysema include di minished chest expansion diminished tactile fremitus and a hyperresonant percussion note faint breath sounds and a barrel shaped chest although the last is by no means specific Cyanosis is common in moderate emphysema but when it is severe right sided cardiac failure is generally present Degree of polycythemia and finger clubbing is in rough proportion to the degree of cyanosis

Symptoms of emphysema may simulate those of right sided heart failure making early diagnosis of right ventricular failure difficult Dyspnea central cyanosis cough jugular vein distention and a palpable liver may occur in both However a hepatojugular reflux or tenderness of the liver is evidence of cardiac failure Angina hypercyanotica may accompany emphysema and closely mimic angina pectoris Syncope may result from the cerebral anoxia consequent to prolonged coughing Edema of the ankles generally indicates right sided failure although some authorities attribute it to emphysema itself the anoxia producing increased capillary permeability The signs of right ventricular hypertrophy are often masked by the emphysematous lungs

The usual radiologic appearance of emphysematous lungs and dilated pulmonary artery segment may be somewhat modified by concurrent systemic hypertension and left ventricular hypertrophy Sometimes the descending branch of the left pulmonary artery can resemble a prominent pulmonary conus

ECG evidences of right ventricular hypertrophy the right ventricular strain pattern and right axis deviation are common in chronic pulmonary heart disease Probably the earliest sign of cardiac damage from chronic lung disease is the peaked P waves (P pulmonale) commonly 2 3 mm tall and never widened and thought to result from increased right auricular pressure

Cardiac catheterization studies have shown that in obstructive emphysema without cardiac failure the right ventricular systolic pressure is elevated the diastolic pressure normal when pulmonary heart disease supervenes the ventricular diastolic pressure and the right auricular pressure rise Arterial oxygen saturation is generally 60 80% and the cardiac output may be raised to 5 9 L /minute

Antispasmodics (e g epinephrine nor epinephrine ephed

rine) may be used to control bronchial spasm A sulfonamide or broad spectrum antibiotic should be used immediately to combat infection For deficient chest expansion breathing exercises may be helpful and an oxygen tent may be of benefit when cyanosis of central origin is severe Digitalis should be administered cautiously Theophylline ethylenediamine is a bronchodilator and also dilates the coronary arteries if given intravenously If obstinate failure persists despite these meas ures thiouracil will lower oxygen consumption Use of mor phine and venesection is contraindicated

Treatment of Pulmonary Embolus with Ganglioplegic Agents J P Crosetti C A Muller and J Pettavel (Neu chatel) formulated the hypothesis that if the sympathetic synapses through which the vasoconstrictive reflex originating in an embolized artery passes were blocked with ganglioplegic agents the condition of shock with its accompanying symp toms of severe pain anxiety and dyspnea would be overcome, and classic antalgic therapy with morphine oxygen and heart stimulants would not be needed This hypothesis was tested in 10 patients with acute pulmonary emboli all of whom were relieved of pain after intravenous injection of 100 mg pen diomide usually at the rate of 20 mg/min No other medica tion was given Relief was rapid occurring within 15 minutes in three patients and was complete within 30 minutes in all but one This patient who had had a colostomy for a sigmoid carcinoma was given an additional 100 mg intramuscularly 15 minutes after the intravenous injection complete sedation resulted within the hour No harmful secondary effects on blood pressure were observed nor did hypotension exceed 31% of the initial values except in a single case in which the drug was given too rapidly Variations in the pulse were negligible The authors consider this the treatment of choice for pulmonary emboli in the initial phase

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CEREBRAL CIRCULATION

Effect of Theophylline with Ethylenediamine (Amino phylline) and Caffeine on Cerebral Hemodynamics and Cere brospinal Fluid Pressure in Patients with Hypertensive Head aches John H Moyer Arthur B Tashnek Sam I Miller

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Harvey Snyder and Russell O Bowman[3] (Baylor Univ) studied 13 patients who were given either 0 5 Gm aminophylline or 0 5 Gm caffeine sodium benzoate intravenously in saline The effects on cerebral blood flow cerebrospinal fluid pressure and the headaches were evaluated Both drugs caused prompt relief from headaches in most patients Aminophylline caused an average drop in cerebrospinal fluid pressure from 210 to 132 mm water With caffeine administration there was an average fall from 172 to 141 mm Cerebral blood flow fell from 53 to 36 cc /100 Gm brain/minute after aminophylline and less after caffeine administration Jugular venous pressure declined with aminophylline but was unaffected by caffeine

Although the mechanism of hypertensive headaches is at present unexplained fully it is thought not to be related to either level of blood pressure alone or cerebrospinal fluid pre sure alone The headaches are likely the result of distention of the cerebral arteries with pain referred to the cranium The increased cerebrovascular resistance and decreased cerebral blood flow after use of these two drugs indicating cerebral arterial constriction caused increased tone and decreased distention of the blood vessels This may well be the genesis of pain relief If hypertension in the cerebral vascular system is transmitted to the postarteriolar capillaries transudation and cerebral edema with so called encephalopathic headaches may occur After aminophylline or caffeine administration there is temporary increase in tone and increased cerebrovascular resistance thus decreasing arterial vascular distention and resulting in less pressure being transmitted to the post arteriolar capillaries This favors return of fluid from the interstices of tissue back into the vascular bed with lessening of the edema and relief from the headache

Histamine Therapy in Acute Ischemia of the Brain Report of 50 New Cases A R Furmanski[4] (Los Angeles) evaluated results by expressing the impairment of neurologic function in terms of units of dysfunction Patients with gross cerebral hemorrhage cerebral edema intracranial neoplasm and terminal cardiac failure were not included Histamine was administered as 5 5 mg histamine phosphate in 1 000 cc of 5% dextrose in saline with modification of the vehicle appropriate for patients who required fluid restriction diabetics or patients

(3) Am J M S 224 377 385 O tob 1952
(4) A M A A h Neur l & P y h t 69 104 117 J ry 1953

on low salt diets Speed of infusion was adjusted to the rate necessary to produce facial flush but no greater since capillaries of skin and brain are considered to be those most sensitive to action of histamine Infusion was begun at 20 drops/minute and if facial flush was not immediately noted slowly increased Seldom was 80 drops/minute exceeded The correct rate was found to be fairly constant for each patient from day to day Histamine was given for four to six hours twice daily until improvement had been maintained for two or three days with two weeks therapy usually considered sufficient to demonstrate that a patient was unresponsive With the histamine 50 100 mg nicotinic acid was given every three hours if feasible

Moderate to pronounced improvement was found in 76% of the patients Seven of the 12 patients who showed no improvement died 5 of heart failure and 2 of failure of the brain Two others died of coronary thromboses but had recovered well from cerebral ischemia before death Patients with least dysfunction had best results from histamine treatment of 23 persons stuporous or comatose (considered evidence of bilaterality of disease) 52% showed improvement Of patients who showed insignificant improvement 92% had stupor or coma—a degree of dysfunction frequently indicating failure of systemic circulation which strongly mitigates against successful treatment of cerebral ischemia with histamine Cardiac insufficiency was present predominantly among patients who showed no improvement Early treatment was of considerable benefit and old age limited possibility of improvement

Use of histamine in these patients was predicated on the assumption that by its vasodilatory effects it both increases the size of the functioning circulation and opens collateral channels—both effects increasing the exposed area of blood combating the stagnant anoxia When anoxic anoxia coexists —as with cardiac insufficiency and pulmonary edema—benefit derived from histamine would be correspondingly decreased Whether the direct effector of physiologic cerebral vasodilatation in ischemia is the body s own histamine or the acid metabolites consequent to anoxia histamine administered intravenously probably can augment vasodilatation and aid the body s mechanisms during reversible cerebral ischemia

When cerebral ischemia is focal there is no physiologic stimulus to capillary dilatation in surrounding

and intravenous use of histamine can be expected to produce its greatest benefit in such patients Generalized stagnant anoxia producing a generalized vasodilatation of the capillary bed of the brain is often accompanied by circulatory failure and response to histamine is limited

Changes in Cerebral Vascular Resistance of Man in Experimental Alkalosis and Acidosis Cerebral vascular resistance in man may be primarily under chemical control Previous studies indicate that neurogenic stimuli hormonal influences and most drugs have little ability to dilate cerebral vessels significantly The potent chemical regulators which dilate cerebral vessels have been shown to be anoxia and either CO retention or decrease in the pH of arterial blood Which of these latter two mechanisms is responsible for increased cerebral blood flow is the subject of a study by James F Schieve and William P Wilson[5] (Duke Univ)

METHOD—Metabolic alkalosis was produced by intravenous infusion of 1 000 ml of 3% sodium bicarbonate or 100 ml of 1 2% sodium bicarbonate over a one hour period Metabolic acidosis was established by slower infusion of approximately 350 cc of 0 8% ammonium chloride over a 60 90 minute period Control studies of blood volume changes were done with infusion of 1 000 ml normal saline in one hour Effect of hypertonicity was observed after administration of 1 000 ml 2% saline in one hour Cerebral blood flow (CBF) was measured by the nitrous oxide technic Arterial blood pH was measured anaerobically with a glass electrode and a Beckman pH meter

Normal saline infused intravenously did not affect CBF or blood pH Infusion of hypertonic saline caused a statistically insignificant increase in CPF and caused no greater hemodilution than isotonic saline However infusion of 3% sodium bicarbonate caused a 65% increase and of 1 2% sodium bicarbonate a 30% increase in CBF suggesting a quantitative action of the bicarbonate The increased CBF caused by 3% sodium bicarbonate was comparable to that found during respiratory acidosis caused by inhalation of 5% CO_2 although the arterial blood pH varied in opposite directions In both cases total CO content of the blood was increased Increase in CBF after sodium bicarbonate infusion is not due primarily to changes in intravascular volume because an equivalent degree of hemodilution produced by infusion of isotonic saline solution does not cause an increase in CBF

(5) J Clin I t 3 33 38 Ja y 1953

Metabolic acidosis reduced CBF and decreased blood pH This downward trend in the CBF was sharply reversed in one patient who inhaled 5% CO_2 after having established the decreased CBF

The participation of the ammonium ion in these result remains to be evaluated but this study indicates when coupled with previous studies by Kety that cerebral vascular tone is more closely related to total CO_2 content of arterial blood than to the arterial blood pH

PERIPHERAL VASCULAR DISEASE

Chronic Obstruction of Abdominal Aorta Report of 30 Cases Bernardo Milanes Rodrigo Bustamante Roberto Guerra Armando Nuñez Nuñez Alfredo L Hernandez Eliseo Perez Stable Jorge McCook and Juan Rodriguez Iñigo[6] (Havana) discuss 30 patients with the Leriche syndrome 5 of them women despite previous reports that only men are affected

Atheroma is almost exclusively the cause of this group of symptoms The disease usually begins with unilateral or bilateral obliteration of the iliac arteries with the thrombotic process progressing centrally until the aorta is completely obstructed *Coldness easy fatigability and weakness of the legs* are generally the first complaints In a more advanced stage symptoms will depend on the condition of the collateral circulation Bilateral intermittent claudication with loss of sustained erection will appear at a more advanced stage Peripheral gangrene appears in 5 10 years after distal extension of the thrombosis Proximal progression of the thrombosis may cause occlusion of the mesenteric and renal arteries Constant physical findings include absence of pulsations and oscillations in the lower extremities and greatly diminished or absent pulsation in both iliac arteries and the infraumbilical segment of the aorta There also are muscular atrophy loss of hair and discoloration in the lower limbs

Clinical and physical signs nearly always suffice for a diagnosis but *differentiation from bilateral obstruction of the iliac arteries* depends on translumbar aortography which helps to delineate the extent of the thrombotic process and in the evaluation of the state of the collateral circulation

(6) Angiology 3 47 48 December 1952

Treatment of the syndrome is disappointing Medical management in the stage of compensated obliteration in 12 patients brought little or no improvement Lumbar sympathectomy was performed in 17 patients and in 5 of them it was combined with aortoiliac resection despite varying degrees of improvement in 8 patients long term results indicated no advantage in combining aortoiliac resection with sympathectomy In ischemic gangrene amputation is hazardous because of the impaired circulation to the stump The authors feel that such advanced surgical procedures as endarteriectomy or vessel grafting offer the greatest promise in treatment of the Leriche syndrome

Thrombosis of the Terminal Aorta is more common than is generally recognized and develops insidiously in most patients According to Frank V Theis[7] (Univ of Illinois) it is a pathologic and clinical entity which should be recognized early if surgery is to be beneficial The clinical syndrome should be easy to recognize when occlusion of the bifurcation is complete Diagnosis is based on long standing bilateral peripheral circulatory deficiency fatigability pain in hip and thigh muscles pathognomonic oscillometric readings and calcification of the aorta The skin temperature response to vasodilator tests will demonstrate the adequacy of collateral channels and patent peripheral circulatory vessels

Of 29 patients with this disease all but 1 had hypercholesteremia despite the fact that many patients had been on various low fat diets 7 had diabetes mellitus half had cardiac disease and 55% had hypertension

The primary disease that leads to thrombosis is nearly always atherosclerosis or arteriosclerosis Autopsy specimens have proved that the disease is not confined to the thrombosed area Resection of the terminal artery is therefore not advisable even if the entire thrombosed area could be removed The extent of the disease in the rest of the artery makes closure of the lumen difficult if not impossible and separation of the friable vessel from perivascular adhesions hazardous Collateral vessels and channels through the thrombus whereby peripheral circulation is maintained would be removed at resection Adequate bilateral lumbar sympathectomy is the most satisfactory surgical procedure for occlusion of the abdominal aorta Peripheral circulation is improved skin tem

(7) S g Gy & Obst 95 505 511 Octobe 195

peratures are restored to normal and symptoms are relieved The only medical treatment for thrombus or arterial disease consists of lowering the cholesterol content of the blood The author feels that lipotrophic substances are unsuccessful but low cholesterol diets are mandatory regardless of the blood cholesterol concentration

Obliterative Disease of Abdominal Aorta and Iliac Arteries with Intermittent Claudication Alan Kekwick Lawson Mc Donald and Robert Semple[8] (Middlesex Hosp London) believe that *arterial obstruction above the inguinal ligament is* a more common cause of intermittent claudication than generally recognized Examination of 53 consecutive patients with intermittent claudication showed this area to be obstructed in 8 Of these 8 and 3 others seen by the courtesy of colleagues 10 had iliac arterial obstruction and 1 obstruction of the terminal aorta Diagnosis was made by aortography in seven cases and by arteriographic demonstration of normal lower limb vessels with evidence of obliterative vascular disease *in one In three* diagnosis was *based on clinical and tonoscillo*graphic evidence

Patients with arterial obliteration above the inguinal ligament often have pain on exercise which extends high into the thigh the femoral pulse is imperceptible weak or delayed and there is wasting of the thigh and buttock on the affected side Impotence may be a presenting complaint in aortic obstruction Tonoscillography which records the peripheral pulse volumes shows a diminution in the pulse volumes in the thigh *after exercise In intermittent claudication caused by* femoral or popliteal obstruction pain in the thigh is less common the femoral pulse is not weakened or delayed and generally there is no wasting of the thigh and buttock On tonoscillography after exercise a normal response is obtained i e there is an increased pulse volume in the thigh

Roentgenographic Differentiation of Peripheral Arteriosclerosis According to Edwin N Barnum[9] (Indianapolis Gen l Hosp) each of the two types of peripheral arteriosclerosis intimal (atherosclerosis) and medial (Monckeberg s) can be differentiated by the roentgen appearance of the peripheral vessels Each type has a characteristic type of calcification

(8) Quart J Med 1 185 200 Apr 1 1952
(9) Am J Roentg 1 68 619 6 6 Oct b 105

Both types of arteriosclerosis and calcification may exist in the same artery in which case the denser calcific plaques of atherosclerosis may obscure the finer concentric rings of medial sclerosis

Atheromatous lesions in 33% of males and 69% of females with clinically evident peripheral atherosclerosis will not show calcification If such patients have both types of peripheral arteriosclerosis only the medial calcification will be visualized Atheromas unless they contain calcium will not show up on x rays When there is calcification it is in plaque form in the intima The atheromas encroach on the lumen of the vessel producing all grades of thrombosis and gangrene Medial sclerosis by definition is always characterized by calcification in the media in the form of trachea like rings This sclerosis does not compromise the lumens of the vessels

When x rays reveal diffuse medial calcification in the arteries of patients who have no symptoms of peripheral vascular obstruction calcium itself has no clinical significance Roentgen evidence of dense plaques of atheromatous calcification scattered along the course of a peripheral artery indicates narrowing of the artery by atherosclerosis but medial calcification if also noted is of no added significance

Treatment of Intermittent Claudication was evaluated by M Hamilton and G M Wilson[1] on the basis of results in 40 patients Effectiveness of treatment was measured by the performance of the patient walking at his ordinary pace over a pair of steps 18 in high Although not all factors are under full control the test has the advantage of familiarity to the patient and results are not affected by variations in skill of performance Observations included the number of circuits traveled when pain developed and the time taken to walk them the average rate at which each circuit was completed and the time taken for pain to subside with the patient standing still Two types of therapy were employed—long term treatments extending over several weeks with evaluation at the end of that period and short term treatments in which a drug was given and the patient was exercised while the effect was at a maximum

One form of long term therapy was intermittent venous occlusion produced by a machine The improvement in patients

(1) Q t J Med 1 169 183 Ap l 195

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(8) Q t J M d 2 185 00 Ap 1 1952
(9) Am J Roe tg 1 68 619 6 6 O t b 195

method is simple has obvious advantages and carries no danger of overheating the limb

Changes in cutaneous temperature within the boot as measured by copper constantan thermocouples were observed in 11 patients with and without vascular disease while in a room of constant temperature and humidity After completion of the test which lasted 1½ 3 hours there was a mean increase of 4 8 C (8 8 F) over the control value there was some increase in temperature in every instance An increase of at least 3 1 C (5 5 F) occurred in seven instances two of the four patients with less increase than this had chronic occlusive arterial disease and one had a low BMR (—18%) A patient with Raynaud s disease had an increase of 11 9 C (21 4 F) and one with thromboangiitis obliterans and one with arteriosclerosis obliterans each showed a significant increase in cutaneous temperature An accumulation of 1 Gm or more of sweat was noted on 9 of the 11 patients including 2 with severe ischemia of the limbs

In another series of patients on whom the boot was applied similarly there was a mean increase in blood flow of 0 37 cc / 100 cc tissue/minute as measured by the plethysmokymograph this represents an increase of 24% over the control value No change in blood flow was noted in one patient and an actual decrease occurred in three (two were normal and one had lymphedema precox) in these patients there was an insignificant or borderline change in cutaneous temperature Only four patients in this group had a substantial increase in cutaneous temperature (thought by the authors to be due to a delay in measuring the temperature and other technical factors) three of these had a significant increase in blood flow The pulse volume increased in four instances in three of which both cutaneous temperature and blood flow to the limb increased

The authors feel that if this preliminary report is substantiated by further appraisal use of such a plastic boot may be an effective and harmless way to increase blood flow to the extremities *It may be useful in prophylaxis of postoperative* thrombophlebitis and in the treatment of occlusive peripheral arterial disease vasospastic disorders and thrombophlebitis

treated with bed rest and occlusion might well have been the result of the rest Patients who were ambulatory and used the venous occlusion machine frequently while maintaining ordinary activity *were not benefited The following regimens* were used for long periods with no consistent benefit vitamin E 400 mg daily priscoline* 25 mg four times daily by mouth nicotinic acid 100 mg four times daily by mouth methyltestosterone 5 mg twice daily orally papaverine hydrochloride 2 gr four times daily orally aminophylline 0 2 Gm four times daily orally dihydroergotamine 0 7 1 ml of 15% solution daily by mouth

Heavy smokers who gave up smoking completely and suddenly showed no increase in exercise tolerance after two months Lumbar sympathectomy done on two patients produced no significant improvement Tenotomy was performed on four patients Relief from intermittent claudication was offset by residual disability of varying degree in each

Short term therapy included glyceryl trinitrite (1/120 gr) sublingually epinephrine 0 6-1 2 mg subcutaneously nicotinic acid 50 mg intravenously tetraethylammonium bromide 75 mg intravenously priscoline* 25 mg intravenously dihydroergotamine 1 mg intravenously and padutin* 4 6 units intravenously All failed to cause consistent and unequivocal improvement

A wide variability of exercise tolerance was found from day to day in the same patient as well as spontaneous improvement and improvement attributable to bed rest These factors must be taken into consideration before any success is attributed to specific therapy

Method for Increasing Blood Flow to Extremities by Simple Conservation of Body Heat Preliminary Report of Effect of Insulated Plastic Boot Applied to Lower Extremities Kenneth R Woolling Edgar V Allen Grace M Roth and Khalil G Wakim found that an insulated plastic sleeve applied to the lower extremity as a high boot increased cutaneous temperature digital pulse volume and blood flow in a number of patients by simply conserving body heat The boot consists of an inner and an outer sleeve Spun glass is used for insulation and the whole assembly weighs a little over 1 lb The

(2) Proc Staff Meet May Cl 27 393-401 Oct 8 195

tolerance as measured by a claudicometer which shows the exact distance walked in yards at any set speed and by immediate thermometric response Only the first five substances were used extensively for results with the others were not encouraging The drugs were given by pressure drip or rapid injection None of the patients had aneurysms and only one had venous thrombosis

A substantial number of patients with intermittent claudication showed clinical and claudicometric improvement but oscillations rarely improved Few patients with ischemic necrosis were better

Vasodilators will facilitate compensatory mechanisms when the pathologic process cannot be reversed as in degenerative arthritis Adequate concentration at the site of the lesion is more readily attained with fewer side effects by intra arterial than by other routes Intra arterial injection of vasodilators is a good alternative to more elaborate surgical procedures Many patients precluded from sympathectomy by age general condition or other criteria can be treated by this method A therapeutic trial of the method may in some instances make surgery unnecessary or it can be used if symptoms persist or recur after sympathectomy

Treatment of Peripheral Arterial Obliterative Diseases and Their Complications by Arterial Infusions of Histamine According to Isidor Mufson (Columbia Univ) histamine is a more powerful vasodilator than pri coline[5] and its effects are more prolonged Vasodilatation is greater with histamine than after sympathectomy The rapid hydrolysis of histamine is a safeguard against serious reactions for relief from symptoms promptly follows treatment The author therefore used histamine intra arterially in 133 patients with obliterative arterial disease of the lower extremities The basic solution was as much as 2 75 mg histamine phosphate in 500 cc normal saline given at a rate of 2 5 drops/heart beat An infusion ideally brings about a pronounced erythema from groin to tips of toes Infusions were given semiweekly or weekly Patients with severe leg infections were similarly treated but with addition of aureomycin hydrochloride—buffered with sodium glycinate (1 mg/cc normal saline or 5% glucose in distilled water

(5) Am J Med 1 680 687 J 195

Clinical Effectiveness of Certain Hydrogenated Alkaloids of Ergot in Peripheral Vascular Disorders The hydrogenated alkaloids of ergot—ergocristine ergocornine and ergokryptine—*individually or in combination of equal parts (hydergine CCK 179)* have been shown to have a vasodilating effect on the peripheral vessels Evidence indicates that hydergine has three modes of attack (1) diminution of vasomotor tone (2) peripheral adrenosympathicolytic activity and (3) direct dilator activity on smooth muscles of the vessels

James E Roberts Leighton L Anderson and Thomas M Parry[3] (Univ of Colorado) report results of hydergine therapy in 72 patients with various peripheral vascular diseases Doses varied from 0 5 to 2 mg orally three or four times daily *Results were impressive Of 35 patients with arteriosclerotic* peripheral vascular disease 27 improved including the 6 who had ulcerative lesions All of 6 patients with thromboangiitis obliterans and 10 with chronic venous insufficiency improved Improvement in ulcerative lesions previously resistant to treatment was striking Response of only three of eight patients with Raynaud s disease was to be expected in view of results with other modes of treatment of this disease No conclusions were drawn regarding the value of the drug in acute thrombophlebitis

Oscillometric and skin temperature measurements were not made as these do not always correlate well with subjective improvement Healing of ulcerative lesions under treatment was considered good objective evidence of the effectiveness of hydergine

Intra arterial Injections in Treatment of Peripheral Vascular Disease J W L Edwards N B Jones K B McConnell H S Pemberton and D C Watson[4] *(Liverpool)* gave intra arterial injections to 57 patients with intermittent claudication and 27 with ischemic necrosis using one or more of the *following substances* acetylcholine alcohol histamine papaverine tolazoline (priscoline®) epinephrine atropine nikethamide curare cytochrome C gallamine triethiodide hexamethonium hydergine sodium nicotinate and procaine Improvement was assessed clinically (including evidence of ulcer healing) by oscillometric variation by increased exercise

(3) Am J M S 4 431-438 Oct 4 195
(4) B M J 2 808 811 Oct 11 195

juncture—where it usually stops—thrombectomy is necessary

It is important to suspect hidden thrombophlebitis in the deep veins whenever there is such a process in the superficial veins and one should assume this to be present particularly when there is clinical evidence suggestive of deep venous involvement or when pulmonary embolism has occurred In such cases there should be exploration of both saphenous and femoral veins

For regional heparinization after venous thrombectomy the author uses a polyethylene catheter tied in the stump of the superficial femoral vein and irrigates with 500 cc each of water and saline containing 50 mg heparin in each 500 cc solution Systemic coagulation time is maintained at about eight minutes

Acute thrombophlebitis of the superficial system may be an early sign of thromboangiitis obliterans There will gen erally be evidence of coexisting arterial insufficiency and the signs may be indistinguishable from migratory phlebitis For this condition saphenous ligation or stripping is contra indicated Use of tobacco is interdicted a lumbar sympathec *tomy is performed and the patient is then put on anticoagulant* therapy

Migratory phlebitis like thromboangiitis obliterans may involve the smaller veins of the foot or ankle although it may also involve the main long saphenous trunk or even the deep veins usually in a segmental distribution Surgery is contraindicated The patient is put on anticoagulant therapy and use of tobacco is forbidden

Recurrent thrombophlebitis may be the first sign of obscure visceral malignant disease usually of the pancreas or lung The mechanism is not known although tumor emboli setting up irritant foci in the venous end of the capillary loops may initiate thrombophlebitis

Modern Concepts in Treatment of Postphlebitic Syndrome with Ulcerations of Lower Extremity are discussed by Robert R Linton[7] *(Massachusetts Gen l Hosp) The sequelae of the* thrombotic state which constitute the postphlebitic syndrome including chronic ulcerations develop because of impaired function of the venous heart of the leg Effective treatment is based on restoring the physiologic mechanism at least

(7) A g I gy 3 431 439 D mb 195

with as much as 500 mg aureomycin in each infusion)—or crystalline penicillin to the infusate

Improvement was measured by increase in walking tolerance as reported by the patient and by diminution in night pain in the legs

In 107 patients (group I) the popliteal pulses were not present 89% of the patients were benefited Of 10 patients with no femoral pulsation (group II) 7 were helped by the vasodilatation There were 34 patients in the two groups who could not sleep at night because of leg pains 33 reported complete relief Severe infection complicating peripheral arterial disease was successfully controlled in 13 of 16 patients treated The typical course in patients treated with histamine intraarterially was progressively increasing improvement with each infusion then stabilization with no further improvement but with effects persisting despite little or no further treatment This pattern is assumed to reflect the anatomic development of adequate collateralization Expansion of infected tissues as a result of the histamine induced hyperemia is painful but procaine block of the involved area permits continuation of treatment

Treatment failures resulted from several causes (1) inadequate collateral arterial system (2) extravascular complications (orthopedic neural and pyogenic or fungus disease) (3) the presence of edema which prevented utilization of collateral circulation and (4) continued use of tobacco by patients with thromboangiitis obliterans

Significance and Management of Acute Spontaneous Thrombophlebitis in Superficial Veins of Lower Extremities Eugene L Lowenberg[6] (Norfolk Va Gen l Hosp) found in 49 patients with acute spontaneous thrombophlebitis in superficial veins of the lower extremities simple thrombophlebitis in varicose veins in 26 associated thrombophlebitis of the deep veins in 15 Buerger s disease in 3 migratory phlebitis in 4 and bronchogenic carcinoma in 1

Immediate high saphenous ligation with stripping and resection of venous varicosities is recommended for simple thrombophlebitis occurring in varicose veins Resection is not contraindicated because the inflammation is not infectious If the thrombophlebitic process extends to the saphenofemoral

(6) J I ter t C ll S ge s 18 4 434 Octobe 1952

advantage of being performed on ambulatory patients When the newer sclerosing agents are used (in particular sotradecol*) and with careful technic complications are rare Sigg makes injections without use of tourniquets above or below the site of injection and with the leg in a horizontal position with the veins collapsed thus favoring chemical action where the venous flow is most sluggish and the agent is in contact with the vessel walls longest Duration of treatment is not necessarily longer than with surgery and cosmetic results are better

Superficial and deep phlebitis can be successfully treated with compression bandages thereby channeling some of the blood into the deeper veins promoting competency of the valves and (particularly when used with sponge rubber foundation) surrounding the embarrassed veins with a rubber heart which acts as a pump for the poor circulation

Phlebitic leg ulcers are managed successfully with ordinary saline dressing and a compression bandage which by reducing the edematous tissue surrounding the ulcer brings the levels of skin and of granulation tissue in apposition and promotes epithelization Compression bandages are efficient prophylaxis against embolism

The author feels that some of the adverse opinions regarding sclerotherapy are based on results following improper technic or after use of sodium morrhuate

Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins Follow up Report Raymond Boller Antonio Rottino and Gerald H Pratt[9] (New York Univ) gave 60 140 mg adenosine 5 monophosphate (My B Den) weekly to 40 patients with ulcers and dermatitis associated with varicose veins or the postphlebitic syndrome including 5 with acute thrombophlebitis All had had previous therapy of various types (elastic bandages potassium permanganate baths hot packs and rest) but after muscle adenylic acid therapy was begun only elastic bandages were permitted Therapy continued from a week to several months gave consistently good results in patients who continued the program of treatment as directed The authors consider the therapy a valuable adjunct to surgical treatment of venous disease

(9) A g l gy 3 61 66 J 1952

in part It is believed that destruction of the venous valves of the deep and communicating veins of the leg results in venous engorgement and venous hypertension impairing the function of the venous heart and causing increased lymph formation and lymphedema Edema pain varicose veins skin pigmentation stasis dermatitis chronic induration and chronic ulceration follow

Compression bandages to restore the function of the venous heart of the leg constitute temporary preoperative treatment The author recommends applying a thick gauze dressing with white petrolatum on the leg after it has been painted with an alcoholic solution of resin The leg is then bandaged with a 15 yd 4 in wide gauze bandage with a thick layer of cellucotton incorporated in the bandage by wrapping it around the lower third of the leg and placing an additional thick layer over the ulcer area itself The elastic adhesive dressing is then tightly applied beginning above the ankle covering it the heel and the foot to the base of the toes and is carried up the leg to the level of the tibial tubercle and back down again to the ankle Ambulation is encouraged The dressing should not slide or bind and by compressing superficial venous pathways forces the blood and the flow of lymph upward during muscular activity

Surgical treatment entails removal of all superficial veins in subcutaneous tissues (long and short saphenous and many of their large tributaries) severing of most communicating veins especially on the inner side of the lower leg by division and ligation the interruption of the long column of blood in the valveless deep veins by ligating and dividing the superficial femoral vein just distal to its junction with the profunda femoris and excision of some of the deep fascia of the lower leg (modified Kondoleon procedure) Postoperatively the patient always wears an elastic stocking during the day The results of this method have been encouraging but further observation is necessary to determine whether such extensive surgery is justified

Treatment of Varicosities and Accompanying Complications According to Karl Sigg[8] (Women s Hosp Basel) sclerotherapy of venous varices has no higher incidence of complications or recurrences than surgery and has the distinct

(8) Angiology 3 355 379 October 195

lus serving to mobilize calcium from the bones and tending to restore plasma calcium

Similar adaptive mechanisms may operate in the excretion of water For example the urinary sodium in renal failure may be hypotonic with respect to plasma sodium If water excretion is simply a process of filtration and absorption then this imputes to an ostensibly failing kidney the ability to reabsorb a highly concentrated solution of sodium more than the normal kidney is called upon to do Although this is an improbable but not impossible situation Platt suggests the active excretion of water as an alternative explanation—a physiologic mechanism with ample justification in comparative anatomy This concept has support not only from other theo retic considerations but also experimentally

In chronic renal failure normochromic anemia regularly develops which varies in severity with the degree of azotemia probably being due to bone marrow depression by an unknown agent Restoration of normal hemoglobin values has never been shown to be beneficial it may even be harmful That this anemia may be an adaptive mechanism is suggested by the consideration that since renal blood flow is reduced in renal failure a higher proportion of plasma tends to restore the normal minute volume of plasma presented to the glomeruli This theoretical consideration is being experimentally eval uated

Acute Anuria with Special Reference to Renal Function Fredrik Berglund Jan Ek and Lars Werko (Stockholm) report six cases of acute anuria in which the following prin ciples of treatment were observed adequate caloric intake (1 500 2 000 cal /day) managed by use of Bull s fat glucose emulsion (600 Gm water 100 Gm olive oil 400 Gm glucose 40 Gm gum arabic making up to 600 Gm water with 2 500 cal) (2) fluid intake limited to the previous day s urine volume plus 700 ml equated with insensible water loss (this being augmented as indicated for fever diarrhea high environmental temperature or activity) and (3) blood replacement for ane mia Diagnoses in the six cases were acute nephritis incom patible blood transfusion vinyl bromide intoxication post abortion shock and concealed hemorrhage (two cases) En dogenous and exogenous creatinine clearances blood non

(2) Act med sc d 144 399 407 1953

Structural and Functional Adaptation in Renal Failure Robert Platt[1] (Univ of Manchester) develops the concept that renal failure should be considered to be not depressed function of the kidney as a whole but, rather extremely efficient function by a renal remnant now too small for its task

One of the characteristic biochemical effects of renal failure which is defined as failure of the kidney to preserve the composition of the extracellular fluid is the retention of urea The increased blood level of urea is requisite to constant daily excretion of urea in the presence of diminished glomerular filtration rate Isosthenuria generally ascribed to tubular insufficiency is a physiologic adaptation to increased solute load i e to osmotic diuresis so that when an osmotically active substance such as urea appears in the tubules in excess it is excreted in dilute solution The few remaining intact nephrons thus are called upon to excrete increased solute loads per nephron their heroic response is manifest in histologically demonstrable hypertrophy as well as in the biochemical laboratory Urea if ingested in considerable quantity while a state of dehydration exists consistently lowers the specific gravity of the urine reproducing in the intact kidney the urea overload occurring in the kidney of the uremic subject This of course does not deny that tubular cells may and do become damaged but points out that isosthenuria occurs also as a result of enhanced tubular activity in renal failure

In renal failure until nearly terminal plasma levels of sodium and potassium remain within normal limits This is accomplished by resorbing a decreased percentage of filtered cation another manifestation of enhanced tubular activity during challenge to the kidneys in renal failure There is also evidence for the active tubular excretion of potassium under similar circumstances The serum calcium level tends to fall in renal failure perhaps as a reciprocal adjustment to retained phosphate poor absorption and increased excretion during acidosis Whatever the relative importance of these mechanisms the low serum calcium level acts as a parathyroid stimu

(1) Brit M J 1 1313 1317 J 21 13 1377 J n 8 1952

administration of water will result in the saving of many lives of patients with acute renal shut down from various causes —Ed]

Extracorporeal Dialysis of Blood in Acute Anuria Importance of β Oxidation in the Kidney Tubules According to I Snapper[3] (Mount Sinai Hosp New York City) extracorporeal dialysis is an important and practical means of facilitating excretion of small molecular or ionic substances which in normal circumstances leave the kidney via glomeruli and are transported by the tubules It is certain that accumulation of at least two dialyzable substances in the blood of the anuric patient threatens life—potassium and inorganic and aromatic acids For the present dialysis should aim primarily to remove these substances Attempts at restoration of normal plasma electrolyte and small molecule content should be made with great caution Catastrophe attends restoration of the hypochloremia of renal insufficiency to normal levels The accumulation of nitrogenous fractions—urea uric acid and creatinine—is probably innocuous and these substances should not be used as yardsticks to measure efficacy of dialysis

References to dialyzing mechanisms as artificial kidneys are perhaps misleading inasmuch as this phase of renal function is but a fraction of the activity of the kidney as a whole The secretory mechanisms of the tubules themselves are not supplanted The metabolic functions of the tubular cells enabling them to reabsorb filtered substances against a gradient are lost in renal insufficiency and not supplied by dialysis Synthesis of ammonia of hippuric acid and of phenaceturic acid are important renal processes It can also be shown that the kidney participates importantly in β oxidation

The syndrome of renal failure is due to loss of the secretory processes and of reabsorption of colloids by the tubules to abolition of synthesis and oxidation by the tubules and to abolition of excretion of small molecular substances Only the last is relieved by extracorporeal dialysis

Treatment of Uremia by Dialysis across the Intestinal Mucosa is described by Robert A Reid and Maurice H Wald[4] A modified Miller Abbott tube was used for dialysis across the intestinal mucosa in 15 enterostomized dogs made uremic by bilateral ureteral ligation The liquid used for dialysis was lactate Ringer s solution in 2 5 10% glucose depending on the

(3) B U N w Y k A d M d 28 6 1 629 O tobe 195
(4) Q t B U N rthw t L M S hool 26 212 218 F B 195

protein nitrogen inulin clearance para aminohippuric acid clearance and filtration fraction were determined

The course of the disease can be divided into four phases (Bull) (1) Onset phase such as a period of severe shock or of toxin activity In the present series no electrolyte disturbance other than acidosis was seen in phase 1 (2) Phase of anuria or oliguria with output of urine less than 1 L/day All partial functions of the kidney are equally decreased There is apparently no difference whether renal injury is due to toxins incompatible blood shock or concealed hemorrhage (3) Early diuretic phase with output over 1 L/day Glomerular filtration rate increases but tubular function is still low The end of this phase is that point at which urine/plasma ratio of urea equals 10 and of creatinine 20 and plasma/urine ratio of sodium and chloride equals 5 Diet in this phase should be poor in protein and adequate in calories and contain sufficient electrolytes to replace losses There was no correlation of the length of this phase with that of the anuric phase (4) Late diuretic phase period of recovery During the year after anuria renal function had returned to normal in five of the six patients

The purpose of the glucose fat diet is (1) to minimize protein combustion and decrease formation of toxic substances which cause symptoms of uremia and of which the blood non protein nitrogen is an index but not a measure (2) to prevent acidosis and (3) to prevent ingestion of excessive ions or fluid during the anuric phase

Control of fluid and electrolyte balance is important and difficult Blood transfusions in the form of exchange transfusions were u ed in some cases as treatment for anemia but not with the aim of removing toxins The arterial needle for bloodletting was left indwelling without untoward effect

[Th importance of avoiding excess administration of water in anuric pati nts cannot be too strongly emphasized Many physicians knowing that the normal kidney responds to water with increased urine volume fail to realize that the same is not true in the case of the abnormal kidney Therefore wl en confronted with a patient exhibiting anuria or oliguria they tend to force water either orally or more commonly as glucose given intravenously Such management does not increase urine volume in most patients and leads to the accumulation of increased water in the body with intracellular edema. At the same time the increase in extracellular fluid volume may cause circulatory failure The amount of water to be given a patient with acute oliguria or anuria should be about 1 L more than the daily urine volume plus the daily loss of wa er through other routes such as vomiting or diarrhea Conservatism in the

change of chemical constituent Irrigation is continued for 12 15 hours and may be safely repeated in 48 hours At the close of the procedure both catheters are used to remove all possible fluid from the abdominal cavity

Fluid compositions depending on the purpose of dialysis are given in Tables 1 and 2 To each liter of fluid regardless

TABLE 1—CO IPOSITION OF IRRIGATING FLUID FOR USE IN RENAL FAILURE*

C M OU	AM U GM /L	COM UN	AM U MEQ /L
NaCl	6 1	Na	130 0
$NaHCO_3$	2 2	K	4 6
KCl	0 35	Ca	4 2
CaCl (anhydrous)†	0.23	Mg	1 1
$MgCl_2$ (anhydrous)	0 05	Cl	115 0
Glucose	20 0	HCO_3	26 0

T tal o m l ty 390 mM /L
†M y b dd d n b lf th m t t p b bly ec y ly t q i b t C ++ th fl d w th d al m th pl m

TABLE 2—COMPOSITION OF IRRIGATING FLUID FOR USE IN CHRONIC EDEMA*

C M OU	AM U GM /L	COM U	AMOU MEQ /L
KCl	0 35	Na	?70
MgCl (anhydrous)	0 05	K	4 6
$CaCl_2$ (anhydrous)	0 23	Ca	4 2
$NaHCO_3$	2 ?0	Mg	1 1
NaH PO_3	0 07	Cl	10 0
Glucose	60 00	HCO_3	26 0
		H PO_4	1 0

T t l o m l ty 405 (515) mM /L

of composition 100 000 units of penicillin 50 mg streptomycin and 5 mg heparin are added to prevent infection and clotting Additional penicillin apart from that in the dialyzing fluid further controls infection Other complications are rare There may be moderate abdominal distention but it will disappear spontaneously or after a small enema or prostigmine® therapy Among contraindications are recent laparotomy peritonitis or superficial infection of the abdominal wall

The primary indication for intermittent transperitoneal dialysis is acute renal insufficiency Removal of 110 Gm urea in 12 hours a figure significant because of the large amount of potassium concurrently abstracted from the body has been reported

{The o ginal attempts to use the pe toneum as a dialyzing mem

state of hydration Two other dogs had dialysis across a surgically isolated loop of ileum Nonprotein nitrogen and blood urea nitrogen concentrations showed consistent lowering concurrent with intestinal dialysis Whole blood chloride serum calcium and protein levels remained constant in the dogs with enterostomy but the hematocrit value and plasma CO combining power declined steadily despite addition of alkalis to the dialyzing fluid or intravenously Blood chloride concentration fluctuated in the dogs with the surgically isolated loop of ileum otherwise biochemical changes were comparable The recovered dialysate in these dogs contained 45 90% of the corresponding blood levels of nonprotein and urea nitrogen

Two moribund patients with renal failure were treated by intestinal mucosal dialysis Large fluctuations in blood chloride concentration were found sodium level was not determined Elevated blood chloride values were corrected by reducing the concentration of sodium chloride in the lavage fluid The recovered dialysate paralleled the blood in concentration of urea nitrogen and nonprotein nitrogen Both patients died a few weeks after hospitalization

Although removal of nonprotein and urea nitrogens from the blood is not necessarily an index of the efficiency of treatment of uremia the authors conclude that transmucosal dialysis in the small intestine is a useful procedure

Short Term Continuous Transperitoneal Dialysis A Simplified Technic that employs only materials readily available in a small hospital is suggested by Marcel Legrain and John P Merrill[5] (Harvard Med School) for treatment of acute renal insufficiency and chronic edema and sometimes as a therapeutic adjunct in chronic renal failure after severe trauma infection or operation

Method —A plain film of the abdomen is first taken to visualize bowel filled with gas or feces Then with the patient prone and suitably prepared with sedatives a trocar is introduced under local anesthesia into the left lower quadrant in the area corresponding to McBurney s point Approximately 2 L of fluid is allowed to run in through a polyvinyl chloride inflow catheter so as to distend the abdomen before the trocar and outflow catheter are introduced on the right The left side is done first to avoid injury to the relatively immobile cecum which is then protected by fluid distention of the abdomen The fluid is allowed to flow in and out of the abdomen at a rate of about 2 L /hour which has been found optimal for inter

(5) New England J Med 248 1 5129 J 1953

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(5) New England J Med 249 1 5 1 9 Jan 2 1953

which intensive use was made of antibiotics and sulfonamides Clinical course and incidence of hematuria azotemia hyper tension and intercurrent infection were studied Pressure in excess of 110/70 was considered abnormal The normal value for serum urea nitrogen was accepted as 19 mg/100 cc Of the 29 children 19 were well 2 were still in an active phase 2 had marked renal impairment and 6 had died In general about half the patients who had hematuria azotemia or hyper tension for periods in excess of two months were either dead or showed evidence of continuing severe renal disease

No attempt was made to differentiate lipid nephrosis and the nephrotic syndrome or the nephrotic stage of glomerulo nephritis on a clinical basis because it was felt that this delineation was inaccurate All patients with edema protein uria lipemia and hypoproteinemia were classified as having the nephrotic syndrome whether or not there was evidence of glomerulonephritis (hematuria azotemia and hypertension)

Children with the nephrotic syndrome appeared more susceptible to infectious diseases (particularly upper respira tory tract infections) and their response to therapy was less favorable than that of the average child Before the use of sulfonamides and antibiotics the major cause of death in this condition was acute infection Despite intensive use of sulfon amides and penicillin severe infections developed in 23 of the patients and 4 died—all of bronchopneumonia In contrast measles was twice observed to influence favorably the course of nephrosis

Death due to infection may be prevented sometimes by chemotherapy or antibiotics Treatment of this syndrome should be directed toward prevention and therapy of infection and maintenance of physical and emotional well being of the patient

Treatment of Nephrotic Syndrome with Interrupted ACTH or Oral Cortisone Therapy was studied by Kurt Lange Law rence Slobody and Ruth Strang[1] (New York Med College) In previous studies it has been shown that serum complement level is low in acute and subacute glomerulonephritis and that in almost all patients with the nephrotic syndrome it is low during the edematous phase rising to or toward normal 24-48 hours before onset of diuresis Conversely complement falls

(1) P oc Soc Expe Biol & M d 8 315 317 F bru ry 1953

tration Treatment was based on the concept that promotion of diuresis was the most important phase of therapy Concentrated low salt serum albumin was given to some producing temporary diuresis and loss of edema Endocrine preparations were tried with inconsistent results Only mercury was a potent diuretic and its use was abandoned because of severe reactions The diet was usually high in protein (up to 3 Gm/kg/day) low in salt and sometimes low in fat Electrolyte balance becomes precarious with copious diuresis and must be watched carefully

Of 33 patients treated before use of chemotherapy 5 recovered 6 were clinically well but had albuminuria 1 was in poor condition and the others died Of 24 treated with concurrent chemotherapy 3 recovered 4 were clinically well but had albuminuria 2 were in poor condition and the others died Of the 21 children who died during the prechemotherapy period 16 died less than a year after onset and 19 died of bacterial complications Fifteen children died after introduction of chemotherapy only five within a year after onset and only one of a bacterial infection Life apparently is somewhat prolonged by use of chemotherapy but the mortality remains about the same

Acute illnesses (particularly measles) in children with lipid nephrosis may be followed by diuresis and improvement or recovery Chemotherapeutic agents used for intercurrent infections interfere with the natural course of infections and subsequent diuresis occurs less frequently perhaps due to inhibition of the patient s antibody formation by early use of exogenous antibacterial factors

Persistent azotemia and rapidly developing anemia were poor prognostic signs On the other hand albuminuria is apparently compatible with long survival

Lipid nephrosis is possibly not primarily a kidney disease there may be some extrarenal factor acting on the kidney as a target organ causing dysfunction of protein absorption

Nephrotic Syndrome in Children Observations on Clinical Course and Influence of Sulfonamide and Antibiotic Therapy Irving Philips Joseph K Calvin and Benjamin M Kagan[9] (Michael Reese Hosp) reviewed the records of 29 children with this syndrome hospitalized during 1944 50 a period in

(9) A M A Am J D Ch 11 85 451 461 Ap 1 1953

ment of patients with lipid nephrosis (1) decrease in proteinuria (2) decrease in physical elements in the urine (3) increase in serum albumin and plasma protein (4) restoration of normal electrophoretic pattern of blood except for gamma globulin which remains low (5) decrease in hypercholesteremia and hyperlipemia (6) reduction in elevated erythrocyte sedimentation rate (7) increase in plasma complement concentration (8) reduction in blood concentration of the antidiuretic hormone of the neurohypophysis (9) increase in glomerular filtration rate and improvement in effective renal plasma flow and tubular function (10) reduction of the abnormal sodium retaining activity of urinary corticoids and (11) restoration of normal capacity of the renal tubules to reject sodium

In 12 patients previously reported on edema recurred within a short time after ACTH treatment in all but one Before dismissal from hospital only the sedimentation rate had been normal with any frequency other tests had shown inconsistent improvement toward but not reaching normal An attempt was made to determine whether it was possible to alter these values further in the direction of normality by administration of ACTH following diuresis and to determine what effect this would have on the course of the disease Eight patients without persistent azotemia hypertension or gross hematuria were given ACTH for 10 17 days Despite lack of clinical evidence of edema a second course of 10 17 days was given a week or two later Dosage was 25 mg every six hours as a rule Prophylactic antibiotics and potassium chloride orally were given

Clinical improvement occurred consistently and normal values were obtained in many laboratory tests before discharge from the hospital Patients had been followed 1½ 8 months when the report was made and all but three were edema free Relapse occurred in three patients after 3 5½ and 5½ months

Complications of ACTH therapy include hypertension hyperglycemia and glycosuria Hypokalemia was seen even with orally administered prophylactic potassium chloride and there is as yet no evidence to indicate whether prophylactic therapy is of value Potassium chloride given orally rapidly restored the deranged electrolyte balance Two patients died during ACTH therapy one had persistent hypertension and

below normal levels one to two days before clinical relapses This behavior is considered the result of a complement binding antigen antibody reaction in vivo wherein the altered kidney (probably the glomerular basement membrane) represents the antigen Urinary excretion of complement is unrelated nor is the low complement level related to proteinuria Normal serum complement by the authors method is 1 3 units Cortisone and ACTH have been shown to depress antibody formation They do not alter serum complement levels in normal animals or in normal man If the assumed complement binding antigen antibody reaction occurs administration of these drugs should effect a rise in serum complement

For seven days ACTH 100 mg /day was given to 4 adults and 12 children with the nephrotic syndrome all of whom had low serum complement levels (average 0 71 unit) Massive diuresis occurred in 22 of the 25 courses of treatment each time preceded by rise in complement In the three instances in which no diuresis occurred serum complement rose little or none Eleven patients relapsed within 12 months in 2 this occurred despite trial maintenance therapy of 25 mg ACTH/day

To minimize relapse incidence interrupted treatment was given six children Beginning five to seven days after the basic treatment 100 mg ACTH was given daily for three consecutive days and repeated weekly on the same days for five to eight weeks Five had not relapsed 6-26 months after treatment One child became edematous four days after onset of severe otitis but an additional seven day course of ACTH was given and edema did not reappear Three patients had no albuminuria hypoproteinemia or hyperlipemia

Three patients were treated with ACTH followed five to seven days later by cortisone orally in a dose of 100 mg four times daily for three consecutive days Cortisone therapy was repeated weekly for five to six weeks until serum complement was stabilized at a normal level or higher All patients were edema free and laboratory evidence of the disease had lessened or disappeared

Treatment of Nonedematous Nephrotic Child with ACTH Benjamin Kramer Herbert Goldman and Louise Cason[2] (Brooklyn) compile these documented results of ACTH treat

(2) J P d t 41 79 803 Dec mbe 1952

with lipid nephrosis has been shown to be subnormal and the consequent hypoproteinemia may lead to edema ascites and hydrothorax These pathologic alterations may in fact be the result of methionine deficiency since methionine plays an important role in total metabolism Fatty infiltration of the liver may be related to lipid nephrosis It has previously been found that rats on a methionine cystine deficient diet have degeneration of the convoluted tubules of the kidneys in addition to liver damage

Methionine is important in detoxification of certain sub stances It enters into sulfur metabolism and has transmethyl ation ability

Goldstein describes the methionine treatment in a single case of lipid nephrosis because the disease is uncommon and with the expectation that subsequent clinical trials of this therapy will clarify its value

Effect of Magnesium Sulfate on Renal Dynamics in Acute Glomerulonephritis in Children was studied by Jerome S Harris and William J A DeMaria[4] (Duke Univ) who com pared results with those obtained in normal children

METHODS —Inulin and para aminohippurate clearances were taken a indicative of the glomerular filtration rate (GFR) and effective renal plasma flow (RPF) respectively Plasma levels were estab lished by intravenous priming and maintenance doses with the PAH plasma level never greater than 3 mg /100 cc After an equilibration time of 0 40 minute three urine collection periods (15 25 minutes each) were established Magnesium sulfate was given intravenously and the plasma level maintained by continuous infu ion Inulin and PAH were determined from cadmium sulfate filtrates of plasma and urine with alcoholic diphenylamine reagent for inulin Magnesium was determined by colorimetric analysis of a magnesium ammonium phosphate precipitate Clearances were corrected to 1 73 sq m body surface

No significant changes in renal functions were noted after magnesium infusion in four normal children Average values obtained for renal functions were GFR 148 cc min and RPF 709 cc /min Effective renal blood flow (RBF) was 1 220 cc /min and filtration fraction (FF) was 0 210

In nine children with acute nephritis in the early hyper tensive phase average values were GFR 82 cc /min RPF 445 cc /min RBF 655 cc /min and FF 0 175 Thus the mean GFR RPF and RBF were significantly lower than nor

(4) Ped tr 11 191 206 M b 1953

chronic glomerulonephritis and should not have been included in the series and the other had convulsions and died after treatment with a long acting ACTH preparation No autopsy was permitted blood chemistry examinations at death were normal

The dosage recommended by the authors for the nephrotic child is at least 150 mg/day/sq m body surface This amount has caused complete diuresis in 16 of 17 trials The dose can be approximated in children less than 5 years old as 3-4 mg/lb/day (dry weight) The effects of ACTH are manifold and the benefit of this drug in treatment of nephrosis probably rests upon many bases Continued treatment under close observation with attempt to restore more of the blood abnormalities to normal appears to result in a lower incidence of relapse and lessened incidence of serious infection Opposing this benefit are additional expense to the family and psychologic trauma to the child

[The treatment of nephrosis has always been unsatisfactory Although the use of ACTH is somewhat hazardous the risks can be minimized by careful clinical and chemical observations This therapy appears to be the most promising of any method of management now available for patients with nephrosis —Ed]

Methionine in Lipid Nephrosis *A Therapeutic Trial* is reported by Louis S Goldstein[3] (Yonkers N Y) who successfully treated a girl aged 2 years and 7 months by use of 9 gr crystalline dl methionine daily Remarkable symptomatic improvement followed with loss of edema lowering of blood cholesterol level restoration of normal concentration of plasma proteins and improvement in signs of renal damage

Methionine is a versatile substance participating in fat protein sulfur and water metabolism Of particular importance in therapy of lipid nephrosis is its ability to enhance protein anabolism promoting nitrogen retention and restoring plasma proteins By virtue of its lipotropic activity it favors transport of lipids in colloidal suspension and prevents fatty infiltration of the liver and probably of the kidneys removing the lipids from the convoluted tubules and encouraging diuresis The rapid reabsorption of sodium in lipid nephrosis considered to be the result of relatively slow passage of the glomerular filtrate through the lipid laden convoluted tubules is decreased

The concentration of amino acids in the blood of patients

(3) Arch P d t 69 366 376 S pt mbe 1952

patient s renal function The authors recommend the following regimen 150 200 mg hydrated magnesium sulfate/kg body weight given slowly as a 3% solution (5 7 cc /kg) in one hour so that approximately half this dose is given in the first 15 20 minutes Limitations are those already noted of blood pressure and clinical response No toxic symptoms were observed when the drug was given in this manner

Mechanism of Isosthenuric Urine Formation in Chronic Glomerulonephritic Kidney M Crepet F Gobbato and P Chiesura[5] (Turin) studied the values of glomerular filtration tubular resorption and urinary elimination of water and total solutes in patients with chronic isosthenuric nephritis paying special attention to the behavior of urea and chlorides They found increased proportional elimination of water and total solutes of a kind present in the normal kidney only under experimental conditions of osmotic diuresis Some such mechanism probably operates at the tubular level in pathologic conditions accompanied by isosthenuria Apparently the distal tubule loses its most characteristic property that of resorbing water against the total osmotic pressure of the urine with the result that the urine finally excreted from the nephritic kidney in its terminal state is the product of a nephron deprived of the functional support of the distal tubular tract

Extreme reduction in glomerular activity and an almost parallel reduction in the number of tubules result in a lack of balance in the nephron in which one element predominates The pathologic changes in the nephron are of two kinds hypertrophic and atrophic Hyperplastic cellular proliferation produces an increase in the diameter and length of the proximal convoluted tubule which suggests that its activity is preserved if not augmented whereas dilatation with pronounced thinning of the walls is common in the distal tubule The comparative integrity of the proximal tubule indicates its predominance in producing isosthenuric urine and shows that other factors which may appear collaterally are in reality superimposed on the essential changes in the nephron This finding is supported by disturbances in the mechanism of acid base regulation and in ammonia genesis both of which are largely functions of the distal tubule

(5) M m d 43 849 857 N 5 1952

mal although the FF was not significantly different from normal

During convalescence patients showed these average values GFR 108 ± 30 RPF 641 ± 157 RBF, 1 018 ± 231 and FF 0 168 The mean effective RPF and RBF were significantly higher than during the early stage and no longer significantly differed from normal the FF had decreased and was significantly lower than normal

Magnesium sulfate was given intravenously to seven patients in the hypertensive phase of acute nephritis generally in a 3% solution at a rate of up to 4 cc /min to tolerance as measured by maintenance of blood pressure sense of warmth or appearance of cutaneous vasodilatation The total amount of magnesium sulfate given was 1 2 5 3 Gm depending upon the size and condition of the child A plasma concentration greater than 5 mg /100 cc was obtained In these patients the GFR increased 3 55% (average 24%) RPF increased 7 76% (average 42%) both significantly greater than normal There was a pronounced fall in FF The experiment was repeated in four patients 5 20 days later during convalescence at which time the patients were clinically much improved and blood pressures were normal At that time GFR was not significantly increased but RPF was increased an average of 30%

The PAH extraction ratio was not increased by magnesium sulfate The drug has no appreciable effect on plasma protein or plasma water concentration and does not have a specific effect on general capillary permeability The authors conclude that the probable mechanism of action of magnesium is to relieve renal vasospasm and effect a real increase in RBF in acute nephritis with hypertension Diuresis after magnesium would therefore be in part an osmotic diuresis and in part the result of increased GFR and relief of renal vasospasm The clinical regression of symptoms of hypertensive encephalopathy consequent to magnesium administration may occur before or without demonstrable change in systemic blood pressure and generally persists after return to hypertensive levels This suggests the importance of cerebral blood flow determination experiments in patients with this disease

Equilibration of magnesium concentration between interstitial fluid and plasma probably occurs rapidly Urinary loss increases with delivery of edema and improvement in the

secondary chronic renal infection and renal tuberculosis Of 100 patients who had undergone nephrectomy specifically for relief of hypertension and who had been followed for two to nine years 64 had significant reduction of blood pressure Of 60 who had been followed five years or more 31 (53%) continued to have significantly lowered pressure Since the blood pressure may become normal after nephrectomy only to return to hypertensive levels after a year or so evaluation of results is hazardous for at least two years postoperatively

Patients subjected to nephrectomy for relief of hypertension should include only those with completely normal function of the opposite kidney and with no history or evidence of disease in that kidney those in good general condition preferably less than age 50 and those in whom duration of hypertension has been relatively short

Diagnosis of Nephroptosis on Supine Pyelogram Recent tendency to neglect nephroptosis completely is unfortunate as displacement of the kidney may result in kinking at the pyeloureteral junction and lead to pyelitis or to prehydronephrosis The vague symptoms of back pain colic relapsing infection and even gastrointestinal disturbance do not suggest nephroptosis and because of this erect films are not requested with the intravenous pyelogram

C B A J Puylaert[6] (Leiden) describes findings which establish the diagnosis on the pyelogram taken with the patient supine A film is taken five minutes after injection of the contrast medium The ureters are then compressed and films are taken every five minutes until a satisfactory anatomic outline is obtained Then compression is removed and two more films are taken The film taken before compression is applied and to a lesser extent the films after decompression show the pelvis in normal condition without tension In nephroptosis the pelvis often seems to have a drooping appearance comparable to that of a withered flower The angle between pelvis and ureter is small sometimes rounded sometimes acute All lines outlining the major and minor calices run downward and lateral The picture of the pelvis itself is spotty and shows lines which run in the same direction When compression is applied the ptotic kidney is moved appreciably upward and the pelvis comes under tension so that the flower as it were blooms again' The finding of such a drooping kidney can always be followed with an erect view which yields further proof

In only 2 of 30 cases which showed a drooping kidney with a pyeloureteral angle of less than 90 degrees ptosis could not be confirmed On the other hand for 76 patients who were known to have nephroptosis review of pyelograms showed 67 with definite 2 with equivocal and 7 with no drooping of the kidney These data satisfactorily establish drooping as a reliable sign of ptosis

End Results Following Nephrectomy in Patients with Hypertension are reported by William F Braasch[7] Unilateral renal lesions most frequently causing surgically correctible hypertension are atrophic pyelonephritis hydronephrosis with

(6) Ned Tijdschr Geneesk 96 2963 868 Nov 15 195
(7) J Urol 68 6-10 July 19

The Digestive System

GEORGE B EUSTERMAN MD

PART V

THE DIGESTIVE SYSTEM

THE ESOPHAGUS

During the past 15 years the profession has become increasingly aware of the significance of esophageal lesions in clinical medicine and surgery The prevalence of esophagitis and its sequelae and the circumstances giving rise to it of esophagogastric varix formation that formidable accompaniment of portal hypertension to less extent of disorders of motility such as cardiospasm and last but not least of carcinoma are occasion for added interest and concern Progress in knowledge of the anatomy and physiology of the organ and pathogenesis of its diseases has been strikingly slow The great need for factual information so that diagnosis and therapy may be enhanced has stimulated much productive research in recent years in which the radiologist surgeon and clinical investigator have figured prominently

It has been said that the literature of esophageal surgery is full of tragedy After a discouragingly slow start the surgery of esophageal carcinoma has made important strides in the last decade Effective technics have been evolved that permit full restoration of anatomic continuity following excision of all segments of the esophagus for carcinoma except that in the hypopharynx The rationale of extensive gastric resection for idiopathic stricture as a routine procedure is still *sub judice* When hydrostatic dilatation fails to cure cardiospasm the extramucosal myotomy of Helle is the most effective current procedure It does away with the alleged hypertonus of the distal segment and there is less risk of recurrent esophagitis and stricture —Ed

Dysphagia Produced by Contractile Ring in Lower Esophagus Franz J Ingelfinger and Philip Kramer[1] (Boston Univ) observed six patients all men with intermittent dysphagia described as a painful sticking sensation sharply localized under the lower sternum The attacks which were moderate to severe occurred only during eating and were usually related to the eating of certain types of foods or improper mastication The sensation of maximal distress and of complete esophageal occlusion lasted from minutes to hours

Radiologically the constriction appeared qualitatively identical in all cases At the point of maximal development it consisted of a sharply demarcated negative shadow a ring like band 2-6 mm wide which intersected the lumen at a right angle to the long axis of the esophagus The constriction

(1) [illegible] 23 419 430 [illegible] 1953

One patient was relieved of dysphagia after surgical removal of the distal 4 cm of the esophagus another was benefited by dilatation of the lower esophagus The other four all moderate cases got along satisfactorily by chewing carefully and following dietary measures

Anamnestic radiologic physiologic and pathologic evidence indicated that the annular constriction was not caused by a fibrous band inflammatory stricture cardiospasm or diaphragmatic hernia If the claim of several anatomists is correct that a physiologic sphincter exists in the esophagus 1 2 cm above the diaphragmatic hiatus the constriction ring may be identified tentatively as an overactive inferior esophageal sphincter The authors hope that the constriction ring described in their six cases may be recognized as a motor phenomenon distinct from cardiospasm in pathogenesis clinical course and prognosis

Study of Esophageal Pressures in Normal Persons and Patients with Cardiospasm J Walker Butin Arthur M Olsen Herman J Moersch and Charles F Code (Mayo Clinic and Found) used a miniature electromagnetic transducer modified for the gastrointestinal tract The effects of the site of the transducer quantity and character of swallowed material and the subject s position were routinely tested The stimulus to swallow was saliva 5 20 cc water or half a cookie

Examination of 247 records from 12 normal persons revealed a characteristic pattern termed the normal swallowing complex which consisted of an initial wave of negative pressure and three subsequent waves of positive pressure (Fig 68) The first pressure change was a small negative dip of short duration that began almost immediately after onset of the swallow This was usually followed closely by a sudden increase in pressure comprising the first positive wave It was followed by a second gradual and at times indistinct positive pressure wave which was usually terminated after several seconds by the abrupt onset of the final wave This rose rapidly to a high peak and declined quickly until it reached the mean basal pressure Typical responses were most frequent when the person swallowed a small amount (5 10 cc) of water and when the transducer was in the mid esophagus

Although many complexe contained all four components

(2) G oe 1 gy 23 278 93 F bru y 1953

was located 2 5 6 cm above the junction of the esophagus and stomach and usually appeared 0 5 2 5 cm above the shadow of the diaphragm (*Fig 67*) After a swallow of liquid the constriction ring did not appear to retard flow nor was the esophageal lumen proximal to the ring appreciably dilated The situation was different when the patient

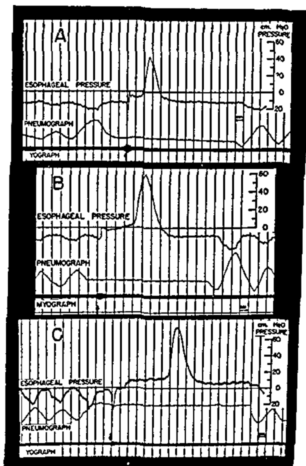


Fig 6 —C t t n ng ju t l d aph gm C a m al f lds th e oph g l gm t d t i t the g ppa nt (Co t y f l g lfi g F J a d K m l C t e t l gy J 419 430 M h 1953)

was given along with barium a portion of food known to precipitate his symptoms As peristalsis pushed the bolus into the lower esophagus the constriction ring narrowed down upon the offending morsel plugging the small lumen at the center of the contraction and the segment of esophagus proximal to the annular constriction ballooned out During this period the patient *experienced the usual distress symptoms* which subsided as peristalsis slowly pushed the obstructing particles past the ring

site in almost all complexes which resulted from swallowing 5 and 15 cc water The mean onset was delayed as the transducer was moved distally beginning at 0 5 0 8 and 1 5 seconds in the upper middle and lower esophagus respectively The mean amplitude varied from 10 to 14 cm water and was greatest in the upper esophagus and when larger amounts of liquid were swallowed The second positive wave occurred in 59% of records most often in the distal (86%) and least often in the proximal portion (33%) Time of onset was related directly to the depth of the transducer being a mean of 1 5 seconds in the upper 2 7 in the middle and 4 4 in the lower esophagus Maximal pressure was greatest in the lower esophagus (21 9 cm water) and with the patient supine The final wave was present in 74% of records It was least common in those from the lower esophagus (59%) Mean time of onset was 2 1 seconds in the upper 5 1 in the middle and 7 9 in the lower esophagus The maximal pressure of the complex was attained at the peak of the final wave in most records mean pressure being somewhat greater in the middle esophagus (66 cm water) than in either the lower (63 6) or upper (49 6) A mean maximal pressure of 100 cm water was attained in records from the middle esophagus after swallows of 15 cc with the patient supine Duration of the total normal swallowing complex varied also with the site of the transducer the shortest (5 6 seconds) being produced in the upper esophagus Swallows in the middle and lower portions produced complexes with mean durations of 9 8 and 12 6 seconds respectively

There were 161 analyzable records in 302 swallows from 10 patients with cardiospasm Fundamental differences noted were (1) the common occurrence of spontaneous phasic pressure changes unrelated to swallowing and (2) lack of a fixed pattern of pressure waves after swallowing Spontaneous motility usually intermittent occurred in 56 records (18 5%) which included all patients with moderate to severe dysphagia The analyzable records were classified into three main groups In the first comprising 32% of responses the complexes resembled normal but there was no clearcut relation between the time maximal pressure was achieved and the position of the transducer in the esophagus In the second comprising 35 5% of responses there was complete absence of pressure changes related to esophageal contraction In the final 15%



F g 68—Typ cal m l w ll w g compl ec d l f om a ou po t of the so h gu A pp po B m dpo t l C l w p t (Court y f B t J W t l (t oe t l g 3 7 93 F bru y 1953)

one or more was absent in about two thirds The initial nega tive wave was noted in 36% of records it was present in about half those from the upper and lower esophagus but in only 16% from the midportion The mean time of onset was 0 1 second after the swallow the mean duration 0 4 second and the mean maximal negative pres ure 5 4 cm water The first positive wave present in 87% occurred often est in the upper esophagus but was present

process with the great omentum hanging down in front like a bib (Figs 69 and 70) In this series 352 patients had sliding and 33 had paraesophageal or mixed types

Paraesophageal hernia may cause gas chest tightness cardiac type pain shortness of breath and anemia from gastric ulceration It may become obstructed or strangulated or may cause no symptoms The syndrome of sliding hernia is fairly well defined flatulent dyspepsia heartburn and postural

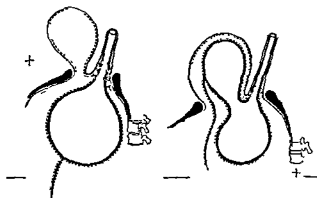


Fig 69 (l ft) —Perito l pou h p g to med t m bet n a d and d ph gm orly w th t t h g of a t r port on of ph enoes phag al l gament. Fig 70 (bt) —I oph g l h rn a Ca d m b low h tu d te l f t m b ll p to p r t e l pou h so th t g eat stu]t m t) be m ppe m t (C rt y f All so I R Ga t t l g 78 333 34 195)

regurgitation The pain of heartburn may radiate behind the sternum into the back into the neck behind the ear to the hard palate and sometimes down the left arm it may be felt while stooping Postural regurgitation is noted particularly when the patient bends forward or is in bed at night Careful x ray study with the patient in stooping or head down position will demonstrate the hernia even then small ones may be missed

Superficial esophageal inflammation may lead to leukoplakia and ulceration and later to dense submucous fibrosis with stricture formation at which time the hernia becomes irreducible Pain is not proportional to macroscopic change and symptoms may remit when the esophagitis remains unchanged Many patients need no treatment other than the

there were multiple phasic contractions in response to a single swallow The remaining records (17 5%) did not fit into any of these categories

The authors conclude that the instantaneous first elevation in pressure of the normal swallowing complex represents the passage of the swallowed material into the esophagus itself probably reflecting the transmission of buccopharyngeal pressure past the recording site The remaining positive waves probably reflect a distally moving peristaltic wave of contraction In patients with cardiospasm the lack of a consistent response after swallowing suggests the occurrence of aimless relatively localized motility in all segments of the esophagus as compared to the consistent propulsive motor activity of the normal organ

[The discussion that followed the presentation of this paper pointed out the advantage of this instrument with one possible exception over the traditional balloon kymograph Enteric motility is measured by direct recording of the pressures that occur spontaneously and which may be responsible for the symptoms presented From the standpoint of the physiologist a defect exists in patients with cardiospasm which prevents them from initiating a standard primary peristaltic wave considered to be the true peristaltic wave This is the wave which apparently opens the door to the stomach which is the cardia Without this key the door so to speak must be forced How the primary peristaltic wave can be restored is the problem and a challenge —Ed]

Nonmalignant Disorders of Gastroesophageal Junction P R Allison[3] discusses hiatus hernia discovered in 385 of 2 500 esophagoscopies performed at the General Infirmary Leeds in 10 years

The function of the cardia is to allow food to pass into the stomach and normally to prevent its return Its competence depends on three main factors (1) the circular muscle fibers at the lower esophagus and their continuance as oblique fibers of the stomach (2) the muscle sling of the right diaphragmatic crus and (3) the oblique entry of the esophagus into the stomach Any surgery or visceral disorder that allows reflux of digestive juices into the esophagus may lead to chronic ulceration and fibrosis The commonest cause of reflux esophagitis is a sliding hernia of the stomach into the mediastinum with the cardia sliding up dragging its ligaments with it and hanging from the lower end of the relaxed esophagus like a bell In paraesophageal hiatal hernia the anterior surface of the stomach may roll up into a peritoneal

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THE STOMACH AND DUODENUM

The year s literature contained the usual variety of subjects of major interest in this field Numerous articles both clinical and investigative dealing with anticholinergic agents indicated that generally speaking these agents proved helpful in about one third of the patients treated. They seemed to be most effective when administered parenterally but this route is not entirely practical As suggested from the outset these agents are useful as adjuncts but not as substitutes for conventional methods of treatment of ulcer if they are well tolerated or not contra indicated There is a prospect that more effective agents will soon be developed

Other items of intere t were the dumping syndrome the differentiation of carc nomatous and benign gastric ulcer treatment of massive hemor rhage and tran pyloric prolap e of the gastric mucosa —Ed

General Adaptation Syndrome (G A S) and Gastroenterology Hans Selye[5] (Univ of Montreal) briefly outlines the G A S as it affects reactions to topical or systemic injury The syndrome is important in many gastrointestinal diseases because of the effects of stress and the adaptive hormones upon the process of inflammation

All agents which act on the body or any of its parts exert dual effects (1) specific actions which are significant as they modify the nonspecific actions of the same agents and (2) nonspecific or stressor effects whose principal pathways are illustrated in Figure 71 The stressor acts on the target (the body or some part of it) directly and indirectly through the pituitary and adrenal Through some unknown pathway a stimulus travels from the target area to the anterior pitui tary which as a result of stress discharges ACTH In many instances this first mediator of hormonal defense may be an adrenaline discharge in others it may be a liberation of histamine like toxic tissue metabolites a nervous impulse or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme)

ACTH stimulates the adrenal cortex to discharge corti coids The prophlogistic corticoids (P C) help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the stressor agent Under ordinary conditions however ACTH causes the adrenal to secrete antiphlogistic corticoids (A C) which tend

(5) R G t 1 0 185 190 M h 1953

understanding that their symptoms have an organic cause Many are too old and debilitated for anything but medical care However when symptoms justify intervention surgery entails repair and suture below the diaphragm of the phreno esophageal ligament peritoneal reflections of the cardia and careful approximation behind the esophagus of the split fibers of the right diaphragmatic crus with minimal injury

Complications in Use of Esophageal Compression Balloons (Sengstaken Tube) In 18 months Hugh D Bennett Lester Baker and Lyle A Baker[4] (V A Hosp Hines Ill) treated with esophageal compression 60 patients most with proved or suspected bleeding esophageal varices Complications from use of the tube arose in five cases causing one death These five cases are reported Complications consisted of posterior pharyngeal obstruction with or without traction on the tube failure of gastric balloon to deflate during removal and ulceration of the esophagus

Most reported complications have been due to attempts to control refractory bleeding by tube traction which led to upward displacement of tube and inflated esophageal balloon into the posterior pharynx and to obstruction of the airway This can be avoided by (1) use of traction only when essential in continued bleeding (2) regulation of tension by weights rather than elastic traction (3) regulation of distance through which traction can act by placing weights just above floor or table and (4) strict supervision by personnel instructed in emergency management

Short traction between the tube at the nares and the adhesive strapping at the chin might be enough In an emergency rapid transection of the tube with scissors deflates both gastric and esophageal balloons allowing immediate and easy removal Direct observation should be used to be sure that both balloons are deflated before removal If easy removal of the tube is impossible tube lumens should be probed Finally since pressure ulceration of the esophagus may develop limitation of tamponade to 72 hours and use of lower pressures if effective in controlling bleeding are recommended

(4) A M A Arch Int Med 90 196-00 Aug t 1952

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systemic stressors the G A S Various combinations of these two basic responses constitute the essence of most diseases

The concept of the G A S holds that many diseases have no single cause no specific pathogen but result from non specific stress and pathogenic situations caused by inappro priate responses to such nonspecific stress Research on stress should follow the theory that we must learn to imitate—and if necessary to correct and complement—the body s auto pharmacologic efforts to combat the stress factor in disease

Crystal Patterns in Dried Preparations of Gastric Juice as Aid in Diagnosis of Gastric Disease In 1933 Henning and Norpoth reported that drops of filtered human gastric juice from fasting subjects which had evaporated on a slide without being stained usually revealed a transparent struc tureless peripheral ring and a central area containing one or more characteristic lattice structures believed to be modi fied crystals of sodium chloride or delicate fernlike structures resembling frost crystals on a window pane The latter were rectangular in normal gastric juice or stellate and poly poid in gastric juice from patients with gastritis and pernicious anemia Because the appearance of these specimens especially in the peripheral zone seemed to be correlated with gastric disease these investigators proposed such microscopic exam inations for diagnosis of gastric pathology

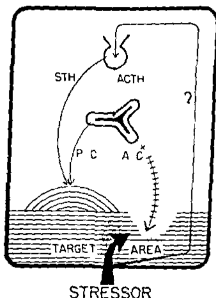
Franklin Hollander[6] points out that there is no direct evidence that the structures in question were sodium chloride modified by extragastric contaminants Moreover the non specific character of such rectangular crystals is generally recognized among crystallographers Identical crystals have been seen in air-dried smears of pure canine gastric mucus stained with toluidine blue or Wright s stain such material was collected from Heidenhain pouches with the mucosa showing no evidence of disease The lattice structures of Henning and Norpoth may have been derived from the normal mucus contained in gastric aspirates or may have resulted from a nonspecific chemical source It seems unlikely that they have any diagnostic significance

Guaiac Test—Correlation with Clinical Findings Roy N Barnett[7] (Yale Univ) examined charts of all patients on

(6) G t oent ology 3 116-117 J ry 1953
(7) Ib d 21 540-543 A gust 195

to cause involution of connective tissue and depress the inflammatory potential thus opening the way to spread of infection

As far as is known ACTH always stimulates the adrenal to produce the various corticoids in the same ratio predominantly A C The pituitary somatotrophic hormone (STH) also increases the inflammatory potential sensitizing the tar



Fg 71 —Rel t n of pitu ta y and ad enal glands to target area in st Prin p l pathw s of ACTH somat troph c h mon (STH) p ophl g t co t o ds (P C) nd antiphlog st rt co ds (A C) a e llustr t d Th unknown p thw y by wh h a t m lus tr vels f om the injured ta g t a to th nt r p t ta y labeled by a qu t on m tk (C u t sy of S lye H Re G st oent r l 20 185 190 Ma h 1953)

get area to the actions of the P Cs Even if ACTH is the only corticotrophin the actions of the corticoids under its influence can be vastly different depending on conditioning factors (such as STH) which specifically sensitize the target for either type of corticoid action Conditioning factors can even alter the response to ACTH of the adrenal cortex itself so that its cells produce more A Cs or P Cs Thus during stress either type of effect can predominate The fundamental reaction pattern to topical stressors is inflammation to

to the stomach or duodenum Commonest symptoms are ab dominal pain or discomfort unrelieved by food or antacid gas belching fulness burning regurgitation nausea vomit ing bleeding weakness and weight loss Symptoms tend to become progressively worse as the mucosa becomes more redundant and the extent of prolapse increases they may be aggravated when the patient lies down Usually there are symptom free intervals and temporary relief after the use of antispasmodics

There is some epigastric tenderness on deep pressure Gastric acid values usually normal range from extremely low to moderately high Gastroscopy may help in differential diagnosis and should be used to exclude other disease al though it offers little to the diagnosis of prolapse Essential pathologic changes are redundant gastric mucosa and gastritis Resected mucosal folds show evidence of chronic gastritis with congestion of the vascular channels and lymphocytic infiltration Commonly associated conditions include gastritis peptic ulcer and hiatal hernia Duodenitis is rare Character istic x ray findings include (1) mushroom cauliflower umbrella like or lobulated defect in the base of the duodenal bulb (2) honeycomb or mottled defect in the bulb produced by the intraduodenal gastric mucosa (3) variations in the appearance of the duodenal bulb in the same and on repeated examinations (4) disappearance of the duodenal deformity when prolapse is reduced (5) absence of irritability of the bulb when not associated with ulcer (6) accelerated gastric peristalsis (7) enlargement and disorientation of gastric mucosal folds associated with hypertrophic gastritis and (8) gastric folds prolapsed into the bulb In differential diag nosis prolapsing neoplasm carcinoma peptic ulcer hyper trophic pyloric stenosis hypertrophic gastritis and invagina tion of the pylorus into the duodenal bulb must be excluded Prolapse most often simulates atypical duodenal ulcer but differs in that pain is aggravated by food alkalis fail to relieve there is no night pain it occurs in older persons hyperacidity is usually absent there is greater tendency to nausea vomiting and hematemesis and a higher incidence of gas abdominal fulness and weight loss

Prolapse of the gastric mucosa is ordinarily a medical problem Antispasmodics anticholinergic and ganglionic

whose stools guaiac tests were done between February 19 0 and June 1951 in the Norwalk Conn Hospital and selected 168 for analysis

METHOD—Several drops of glacial acetic acid and 5 8 cc 3% hydrogen peroxide are added to a pinch of gum guaiac dissolved in 5 cc of 95% alcohol The mixture is then added to 0 5 Gm stool emulsified in distilled water A positive reaction is a blue color developing in one minute

Of 255 tests on stools from the 168 patients only 57% gave false positive results i e showed blood without known cause other than small traumas as from tooth brushing nose bleeds and excessive ingestion of meat by some patients Of those tests on stools expected to show blood from known lesions 96 5% gave positive results

In another series of 41 specimens from 24 patients with malignant disease of the esophagus stomach intestine colon rectum pancreas and biliary tree only 22 were positive by the guaiac test 12 of the patients had never had a positive result It is not surprising that half of these patients with proved gastrointestinal cancer would have been overlooked in a survey based only on stool tests for blood since bleeding from such lesions is irregular or not present A more sensitive test for occult blood would have detected bleeding of lesser degree but would have increased the percentage of false positives to a prohibitive extent The guaiac test should therefore be reserved for its well merited role in clinical medicine and should not be considered a screening procedure for cancer

Clinical Evaluation of Prolapse of Gastric Mucosa into Duodenum According to Maurice Feldman Samuel Morrison and Philip Myers[8] (Baltimore) incidence of this condition ranged from 1 8% among 20 467 gastrointestinal roentgen examinations to 14% among 371 consecutive patients with gastrointestinal symptoms The chief causes are redundant and excessively mobile antral mucosa gastritis involving the antral mucosa with mucosal hypertrophy and heightened peristaltic activity The condition is found oftener in older persons and predominantly in men Clinical manifestations often indicate pyloroduodenal disturbance but like other intermittent disturbances may produce no symptoms or may be an incidental finding in patients with disease unrelated

(8) Gastroenterology 2 80 102 September 195

after acid intake and 18 experienced relief of spontaneous pain within a few minutes There was no constant relationship between the fasting level of acidity and the presence or absence of pain in the 25 patients studied

Of the 66 patients studied by fluoroscopy after acid barium intake 27 had positive and 39 negative results Alterations of normal motility consisting of a delay in gastric evacuation usually accompanied by hypermotility of the stomach were seen in all positive tests Many had persistent spasm of the stomach or duodenum In gastric ulcer patients the spasm was at the ulcer site or just distal to it whereas in most duodenal ulcers the spasm appeared around the ulcer in the postbulbar area or in the gastric antrum Most patients with a negative reaction had normal gastric motility and prompt emptying In the rest gastric motility was sluggish or absent but the pylorus was patent and the stomach emptied readily with the patient in a recumbent right anterior oblique position

The effect of cholinergic blocking agents was studied clinically and fluoroscopically in 26 patients with a positive acid barium reaction with well established pain pattern Twenty four were given 50 or 100 mg banthine® intramuscularly and two received 20 mg SKF* 1637 parenterally Relief from pain was prompt and often dramatic in 25 patients within 2 30 minutes Cessation of peristaltic activity with relaxation of the stomach and pylorus followed drug intake and coincided exactly with relief from pain

The authors suggest that abnormal motility is the fundamental mechanism producing ulcer pain For the production and perception of this pain there must be (1) a stimulus HCl or others (2) an intact motor nerve supply to the stomach and duodenum (3) altered gastroduodenal motility and (4) an intact sensory pathway to the cerebral cortex

Study of Relationship between Motility and Pain in Peptic Ulcer Using Hexamethonium Peptic ulcer pain is believed to be of muscular origin or the result of chemical stimulation of pain nerve endings by hydrochloric acid Differences in nature and severity of pain at time of observation account for the contradictory hypotheses regarding the mechanism of pain The importance of muscular factors can be tested by inhibiting gastric and duodenal motility during pain attacks without changing gastric acidity Hexamethonium bromide

blocking agents will eliminate or control heightened peristalsis A bland diet and psychotherapy to eliminate the cephalic phase of stomach activity may be prescribed Minimal prolapse should be treated to prevent progression to moderate or severe prolapse Surgical exploration is indicated if there is persistent severe pain hematemesis or obstruction Gastric resection is the operation of choice

[Reports of transpyloric prolapse of the gastric mucosa have become increasingly frequent in the past eight years Disagreement persists as to its clinical significance On the one hand there are the high incidence of mucosal prolapse reported in patients without symptoms the frequent association of other diseases of the upper digestive and biliary tract which may be the basis of the presenting complaint and the frequent failure of cure following operation in patients followed for an adequate period of time On the other hand the majority of the observers seem to regard it as a distinct entity and argue that it may be the sole cause underlying the presenting complaint —Ed]

Mechanism of Pain in Peptic Ulcer Two factors which must be considered hydrochloric acid and motility are both variables In this study Julian M Ruffin George J Baylin Clarence W Legerton Jr and E Clinton Texter Jr [9] (Duke Univ) rendered the acid values constant at a high level and observed the relationship between the remaining variable motility and the ulcer pain

METHOD —A series of 100 acid tests with 200 cc of 0 1 N HCl (pH 1) were performed on 88 patients with active ulcer and typical pain within the preceding 24 48 hours In 66 cases 2 oz barium sulfate was added to the HCl The suspension was given orally or by Levin tube and the patient observed by fluoroscopy at frequent intervals for 30 minutes Measurement of gastric acidity before and after introduction of acid or acid barium was made in 25 patients The relations of motility acid barium at the ulcer site and the presence or absence of ulcer pain were studied together with the effects of certain drugs that alter autonomic activity Development of typical ulcer pain or the continuation or accentuation of spontaneous pain after introducing acid constituted a positive reaction A result was considered negative if acid did not produce pain within 30 60 minutes or if spontaneous pain ceased within a few minutes of acid intake

There were 37 positive and 63 negative results Positive reactions consisted of induced pain in 18 cases increased pain in 7 and spontaneous pain in 12 which remained unchanged The highest percentage of positive results was in patients with a lesser curvature (67%) or a channel ulcer (43%) Among those with negative results 45 patients had no pain

(9) G t t l gy 23 52 69 F b y 1953

as sulfanilamide for *50%* inhibition of carbonic anhydrase activity and 440 times as active for *100%* inhibition. Like sulfanilamide it also inhibits acidification of urine.

METHOD.—A series of 18 experiments was performed on three mongrel dogs with Heidenhain pouches 18 hours or more after the last feeding when they had reached basal anacidity or were secreting less than 0.5 ml./hour with a *pH of* 5 or higher. Acid secretion was then stimulated by repeated subcutaneous *injections* of 0.025 mg. histamine every 10 minutes throughout the experiment. After one to three hours, or whenever secretion rate had remained constant for three 20 minute collection periods, compound 6063 was injected intravenously in doses of 5, 10, 20, 30, 40, 60 and 120 mg./kg. body weight dissolved in 0.1 N NaOH. Collection was continued at 20 minute intervals for three to six hours more.

In all experiments with doses of 20 mg./kg. or more there was a sharp decrease *in* volume, in HCl concentration and thus in acid output after injection of compo*und* 6063. Lower doses were effective in only one dog. Secretion was depressed in 15 experiments during the first 20 minute collection period, in 5 during the second, in 2 during the third, *in* 4 and during the fourth in 4. The latent period of 20-80 minutes was inversely correlated with the average *control* rate of secretion. Inhibition persisted two to six hours; recovery was apparently complete 24 hours later. Doses above 20 mg./kg. produced no significant increase in *inhibition* which during the hour of maximal depression ranged from 70-97% (mean *85%*) of the correspond*ing* control value for HCl output. In the range 5-60 mg./kg. the drug was *well tolerated*. However, in another experim*ent* one of five dogs died in respiratory *arrest* after 120 mg./kg.

Results suggest that the inhibition of gastric acid secretion is due to severe inhibition of carbonic anhydrase in the parietal cells and *that* the parietal cell is therefore the source *of* gastric HCl.

[Advances in knowledge of gastrointestinal physiology are of great importance to the physician because of their possible bearing on clinical problems. Significant recent contributions have been *concerned* with problems of the nervous and hormonal regulation of gastric functions and, more particularly, with the formation of hydrochloric acid and the control of gastric secretion. These have practical implications in the therapy of peptic ulcer and allied gastric disorders which has in large measure been directed to the reduction of secretion of the acid.]

The recognized gastrointestinal hormones are gastrin, secretin, pancreozymin, enterocrinin *and* cholecystokinin. Gastrin has been proved to be chemically unrelated to histamine, *but*, like the latter, to stimulate chiefly but not exclusively the parietal cells. Numerous *other* hormones

was found most effective for such tests by E N Rowlands and P H Friedlander[1] (Univ College Hosp London) who observed 25 patients with roentgen evidence of duodenal ulcer 1 with benign gastric ulcer and 1 with acute gastritis Eleven of the patients underwent gastrectomy but no evidence of pyloric stenosis or ulcer invasion was found

METHOD —Two double lumen tubes were used With one gastric contents were aspirated from one lumen and the other ended in a balloon in the second portion of the duodenum One lumen of the second tube entered a balloon in the antrum and the other lumen also drained gastric contents Both balloon lumens were connected through U shaped water manometers to recording pens on a kymograph The sealed glass electrode was used for pH estimates

The tubes were passed two hours after a light breakfast and hexamethonium was given an average of 62 minutes later after the effect of sterile water intramuscularly had been noted in every patient during the control period Although blood pressure often fell a little after hexamethonium no patient complained of faintness while lying down during the tests Since few patients felt pain spontaneously 0 5% HCl was injected intragastrically If pain resulted sterile water was first given intramuscularly and then hexamethonium later As this never gave relief other means were employed if pain was severe Intragastric injections of water aspiration and reinjection of gastric contents and injections of a solution of equal parts of magnesium trisilicate heavy magnesium carbonate and calcium carbonate were used to study motility during attacks of pain

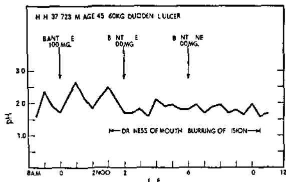
Evidence did not indicate that ulcer pain was associated with increase in tone or short or sustained contractions of the duodenum or stomach Hexamethonium bromide reduced tone and inhibited contraction waves independent of postural hypotension or fainting but did not change the pH of gastric contents Ulcer pain was not relieved by abolishing all contractions or reducing intestinal tone with hexamethonium

Aspiration of stomach contents somewhat relieved and reinjection intensified the pain Neutralization afforded quick and complete relief Attacks of pain in uncomplicated peptic ulcer are apparently not caused by muscular contractions or by increased tension in the stomach or duodenum

Inhibition of Gastric Secretion of Acid in Dogs by Carbonic Anhydrase Inhibitor, 2-Acetylamino 1,3,4-Thiadiazole 5 Sulfonamide (compound 6063) is discussed by Henry D Janowitz Henry Colcher and Franklin Hollander (Mount Sinai Hosp New York City) In vitro it is 330 times as potent

(1) Clin Sc 11 251 265 Aug st 195
(2) Am J Physiol 171 3 5-330 Novembe 1952

ulcer and in 21 normal persons after fasting then after 0 01 0 83 mg banthine®/kg intramuscularly (3) Basal secretion was measured in 21 normal persons and in 15 duodenal ulcer patients after fasting then after 100 mg banthine® orally in 15 cc water (4) After a control period of 1 1½ hours 10 fasting subjects with active duodenal ulcer received 100 mg banthine® orally every four hours for three doses (5) Six patients with active duodenal ulcer were given 100 mg banthine® intraduodenally after a 12 hour fast (6) Ba al



Fg —F l f r t d d se f b th e® lly t d g t d ty (pH) (C t y f L E t J G t oe t l g 1 339 350 J l 195)

histamine tests were performed in 20 patients with duodenal ulcer before and after 100 mg banthine® orally

Studies during insulin hypoglycemia indicate that banthine® intramuscularly in doses sufficient to produce severe side reactions does not completely block parasympathetic postganglionic nerve endings Secretory response never altered significantly from the control study Repeated 100 mg doses of banthine® orally or by intraduodenal tube had no effect on acid concentration in most persons (Fig 72) yet adequate absorption was apparent from the severe side reactions that were almost universal

When the procedure or the oral experiment was duplicated

from the duodenal mucosa have been partially identified or are suspected. The review of the literature on the subject by Hanson and Grossman (Physiol Rev 30 33 1950) is most instructive. Uvnas observations (1942) on the relation between the cephalic and gastric phases of gastric secretion now confirmed in large measure by most investigators apparently represents a milestone in physiologic progress. His observations indicated that neither the hormonal nor the nervous mechanism (vagal) could function independently but that each required the activity of the other. However precise interrelationship between the cephalic (neural) and gastric phases (hormonal) are challenged by Janowitz and Hollander (1951) and by Dragstedt *et al* (1952). A brief though lucid analysis of the various mechanisms by which gastric secretion is normally stimulated has been reported by Thomas in *Review of Gastroenterology*.

Of more immediate interest to clinicians are the mechanism of the formation of hydrochloric acid, the inhibition of acid secretion and inactivation of pepsin in the course of ulcer therapy. Hollander's review of the entire subject is pertinent and timely (Am J Med 13 453 1952). This investigator and his associates state that HCl is the product of hydrolysis of sodium and potassium chlorides which are brought to the parietal cells from the blood by the interstitial fluid. Through the canicular wall H ion from water goes out along with Cl ion that comes from the interstitial fluid and thus emerges as the HCl of the parietal secretion. The corresponding hydroxyl ion from the water passes back into the interior of the cell where it is neutralized immediately, otherwise it would kill the cell in short order. This intracellular neutralizer is chiefly the carbonic acid bicarbonate buffer formed from without and within the cell. Davenport (1939) demonstrated the enzyme carbonic anhydrase within the parietal cell. More recently Hollander and his associates confirmed Davenport's theory that this enzyme plays an important role in speeding up the rate of carbonic formation and neutralizing this hydroxyl ion through the use of a synthetic compound which inhibited carbonic anhydrase in vitro. Diamox also was found to block the formation of HCl in the experimental animals.

Present and past methods of ulcer therapy, pharmacologic or surgical, operated external to the parietal cells. Apart from rest, dietetic measures and psychiatry, they consisted of attempts at adequate neutralization of HCl, blocking or cutting the neural innervation with anticholinergic agents or vagal transection or gastric resection to eliminate the hormonal stimulation of the parietal cells. Even when properly carried out such measures frequently left much to be desired. *Prevention of the formation of HCl within the cell* in whole or large part as has been done experimentally would be the ideal procedure, but it remains to be seen whether this can be successfully accomplished in the ulcer patient.—Ed.]

Effect of Banthine® on Gastric Secretion in Man. Oral, intraduodenal and intramuscular use of the drug was studied by Erwin Levin, Joseph B. Kirsner and Walter L. Palmer[3] (Univ. of Chicago). (1) Insulin tests were performed without and with 25-50 mg. banthine® intramuscularly on separate days in six men with duodenal ulcer. (2) Basal secretion was estimated in 22 patients with duodenal ulcer, 1 with gastric

(3) G st te ol gy 21 339 350 July 1952

banthine® despite its side effects two had no relief with either drug and surgery was recommended and one preferred prantal morning and afternoon because of its minimal side effects and banthine® evening and night because of greater relief Ultimate value of prantal cannot be predicted but 12 of 23 patients using 100 mg doses and 11 of 19 using 200 mg doses had relief of symptoms Some improvement was noted by eight other patients

Reduction of gastric secretions and motility following 25 50 mg intramuscularly equaled results with banthine® Effects on secretions and motility of 100 200 mg orally were inconsistent not equal to the prolonged reduction which followed 100 mg banthine® orally Since reduction of gastric secretions and motility favors healing of ulcer results indicate that prantal will be satisfactory when parenteral administration is indicated It will probably prove inferior to banthine® for oral use since 100 200 mg doses tested were poorly absorbed or relatively ineffective judged by studies of gastric secretions and motility and by infrequent occurrence of parasympatholytic side effects Such side effects were noted with parenteral administration

Effect of Newer Anticholinergic Drugs upon Gastric Secretion in Man Joseph B Kirsner Erwin Levin and Walter L Palmer (Univ of Chicago) performed a total of 359 experiments on peptic ulcer patients and normal subjects all of whom were secreting acid gastric juice continuously under basal conditions The compounds tested—banthine® prantal AP 193 U-0407 U-0385 and U 0229—were given to 165 intramuscularly to 176 orally (via gastric tube) and to 18 intraduodenally Therapeutic efficiency was judged in relation to the effective route of administration dosage rate of gastric secretion and presence or absence of side effects

Each of the five compounds given intramuscularly inhibited the output of acid significantly Quantities usually inducing anacidity were 1 2 2 0 mg for U 0229 1 6 2 0 mg U-0385 and 15 20 mg banthine® Prantal (50 mg) and U 0407 (6-10 mg) temporarily decreased the volume of secretion in all cases and induced anacidity in 80 and 60% The antisecretory potency in decreasing order was U 0229 U 0385 banthine® U-0407 and prantal Anticholinergic drugs given orally were

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except that 25 50 mg banthine® was given intramuscularly pH was significantly affected in 14 of 17 subjects with achlorhydria in 9 Results were similar with banthine® given orally during the basal histamine test

Volume of secretion was significantly reduced in more than half the patients by 100 mg banthine® orally Adequate aliquots for pH estimates became increasingly difficult to obtain Intramuscularly banthine® profoundly depresses basal secretion In doses over 0 02 mg /kg in more than half volume concentration and output of acid were significantly reduced and achlorhydria was common on doses of 0 5 mg /kg or more The effect of the drug was usually apparent in 15-45 minutes and lasted 30 150 minutes Reduction of volume usually reduced that of free acidity and mild to severe side effects usually accompanied an effective dose

The explanation for the superiority of parenteral over oral medication is not apparent The drug may be slightly altered by the digestive processes or the full effect may require the relatively rapid absorption obtained by intramuscular injection

Study of New Quaternary Ammonium Derivative Prantal Capable of Reducing Gastric Secretions and Motility, Tests in Animals and Man, Trial in 44 Patients with Peptic Ulcer C R Rowe Jr K S Grimson and B H Flowe[4] (Duke Univ) gave prantal in varying amounts parenterally to dogs and in 50 200 mg doses every six hours day and night for nine months to patients with peptic ulcers Patients usually continued dietary restriction and occasionally took antacids

In dogs intravenous injections showed that small doses blocked vagal inhibition of the heart and larger doses effected sympathetic and parasympathetic blockade Large doses rapidly injected intravenously reduced systemic blood pressure 7 12 minutes Gastric emptying time and transit time through the small bowel increased with increasing dosage somewhat more than with equivalent doses of banthine ®

During the one to nine month clinical trial results in some patients were encouraging When prantal and banthine® were alternated in seven patients one preferred prantal describing similar relief but less severe if any side effects three with more difficult clinical problems obtained better relief with

(4) G t oe t l gy 21 90 103 M y 195

[Many prominent gastroscopists never use a general anesthetic How ever in selected cases it is conceded that it might be indicated to obtain a better view of the prepyloric area and pylorus to secure a gastroscopic biopsy in the occasional case and in a few of the more difficult esophagos copies General anesthesia may also be desirable in teaching centers where the examination often is prolonged in order to demonstrate technic and findings to students However it has the disadvantage of requiring hospitalization and added expense—Ed]

Gastroenteritis in General Practice Study of 90 Unselected Cases According to W J Smither[7] staphylococcic food poisoning is the commonest cause of the frequent mild cases of diarrhea with or without vomiting seen in general practice Bacteriologic investigation in 74 cases of acute diarrhea by rectal swab and in 16 by rectal swab and inoculum revealed no pathogenic organism in 71 Shigella sonnei was isolated in 14 Proteus vulgaris in 3 and Salmonella typhi murium in 1 Only one patient was hospitalized and diagnosis was food poisoning (toxin type) All others responded rapidly to treatment

The steady annual increase in incidence of food poisoning in England has been attributed to the retention and reheating of meat dishes cooked the previous day the increase in communal feeding where such practices are common and lack of personal hygiene Any of the cases from which no pathogenic organisms were isolated could be due to the heat resistant enterotoxin produced by certain strains of staphylococci which may be extinct in food or rectal swab and yet cause symptoms The ubiquitous distribution of such organisms and the ideal conditions for toxin production in the common cooking practices mentioned support this view The clinical course rapid response to treatment and absence of parenteral infection further tend to confirm it

[Sim lar articles f equently appearing in the literature attest to the interest in and importance of this subject Solomon and his associates have reported their emergency experiences in an epidemic of food poisoning in New York City Feig (Am J Pub Health 42 15 5 1952) contr buted an instructive article with particular reference to methods of nvestigation of food borne outbreaks of acute gastroenteriti It is h ghly probable that the staphylococcus is the chief offender in current outbreaks and that it is ext emely difficult to ascertain the nature of the causat ve organism in ord nary circumstances—Ed]

Ulcer Statistics from Drammen Hospital 1936-45 are reported by Eli Norbye[8] (Hønefors Norway) A total of 1 996 patients was treated for duodenal or gastric ulcers and 863

(7) B t M J 1 376 378 F b 14 1953
(8) Act med d 143 50 6 195

much less effective Only *U-0229* and *U 0385* appreciably inhibited gastric secretion by this route *U 0407* banthine® and prantal were less potent in the order named *AP 193* was totally ineffective Compounds U 0229 U-0385 U 0407 banthine® and prantal did not decrease maximal outputs of acid produced in response to repeated injections of 3 beta amino ethyl pyrazole their administration in advance delayed the secretory response to the histamine analogue but did not suppress it

The incidence and duration of anacidity usually increased in proportion to the incidence and severity of side effects The most potent compounds—*U 0229* and *U 0385*—produced symptoms more often than less effective ones

Use of Anesthetic Agents in Gastroscopy is discussed by John S Atwater[6] (Atlanta Ga) In 245 consecutive gastroscopies equal groups of *122* patients each were given either local or intravenous anesthesia because of multiple drug idiosyncrasies 1 patient received neither Pentothal® or surital® sodium intravenously combined with oxygen intranasally was given to 120 patients and nembutal® sodium intravenously to 2 this was supplemented by d tubocurarine in 115 and syncurine® in 4 Both local and intravenous groups received some local agent except for three patients receiving intravenous drug Pontocaine® 1 2% was given 166 times cocaine 4 10% 71 times and an antihistaminic solution 4 times Most patients received some preliminary medication usually demerol® 75 100 mg or atropine sulfate 0 3 0 4 mg Complete failure of examination occurred only once in either group Incomplete examinations occurred in only three patients receiving intravenous compared to 17 receiving local anesthesia alone

Utilizing the excellent relaxation of the abdominal musculature the gastroscopist could by palpation view the prepyloric area along the lesser curvature and other difficult areas in a greater number of cases with the intravenous approach Moreover this method facilitated the taking of multiple gastric biopsies without added risk or discomfort to the patient When a patient had experienced both types of anesthetic agent he invariably preferred the intravenous method

(6) Gastroenterology 3 60 69 J y 1953

the average males of course preponderating With respect to age at onset there are al o some differences and similarities Note that the Norwegian female with duodenal ulcer i 10 years older than the male In America the ages are almost identical for both sexes But as in America the Nor wegian female with gastric ulcer is older than the male by an average of eight years

The increased incidence of i emorrhage has a familiar ring Manifest bleeding in American ulcer bearing patient during peace time ranges from 20 to 25% In Norway during the period cited hemorrhage occurred in over 33% —Ed]

Multiple Gastric Ulcers Occurring during Phenylbutazone Therapy is reported by Edward C Raffensperger[9] (Harris burg Pa)

Woman 70 with intermittent arthritis for many years had had episodes of upper abdominal distention with excessive belching made worse by eating Four weeks before examination he had been given 200 mg tablets of phenylbutazone and took about 20 in two weeks during which her appetite decreased She stopped treatment because the arthritis improved Several days later she experienced severe abdominal pain with upper abdominal distention Pain increased and radiated into her neck and right upper quadrant A laxative produced a black watery stool

Examination revealed definite tenderness with slight mu cle guarding in the left epigastrium Red cell count was 3 810 000/cu mm with 11 Gm hemoglobin/100 cc White cell count and urine were normal Stool was 4+ for occult blood and fasting gastric juice contained 28 units free and 51 units total acid and 4+ occult bloo l An upper gastrointestinal x ray series revealed a 1 cm ulcer fleck on the anterolateral wall of the upper third of the tomach and a 2 cm niche in the les er curvature at the juncture ot the upper and middle thirds Lar_ge heavy mucosal folds were noted through out the body of the stomach

After 17 d1v cn strict ulcer management x rays showed healing of the anterolateral ulcer and almost complete healing of the lesser curvature one Three weeks later the radiologist reported a com pletely normal stomach

The following aspects suggest that phenylbutazone played a role in formation of these ulcers (1) occurrence of symp toms immediately after use of the drug in a patient with previous gastrointestinal symptoms that were minor and vague (2) location of ulcers in the upper third of the stom ach (3) multiplicity of ulcers (4) severe edema of the mu cosal folds and (5) rapid healing of ulcers and subsidence of edema on ulcer therapy

[The pharmacologic superiority of many of the newer agents over the older ones i e those l sted in the United States Pharmacopeia is fre quently off et by the greater t xi ity of the former In th same issue of

(9) J A M A 15 30 31 M y 2 1953

were discharged with a diagnosis of gastritis or dyspepsia During the first five years duodenal ulcers were twice as frequent as gastric ulcers but during the last five the incidence was *equally distributed* Both ulcers and dyspepsia greatly increased during the war years Duodenal ulcers were far more frequent in men than in women and occurred most often in the former between ages 30 and 40 and in the women 10 years later Gastric ulcers were commonest in men at 40 50 years whereas their *frequency increased with advancing age* in women The incidence of gastritis and dyspepsia was maximum in both men and women at ages 20 30

A total of 368 patients had 460 hospital admissions for hemorrhage There was about an equal number of *patients* with duodenal ulcer gastric ulcer and *negative x ray finding* The group comprised about 16% of all ulcer and dyspepsia patients admitted in the same period Although uncomplicated ulcers were more frequent in men women seemed more *susceptible to hemorrhage Bleeding ulcers were more frequent in the higher age groups where they had poorer prognosis* for recurrence and mortality than in the younger age groups

Mortality was 3 26% (15 patients) Average age of all patients with bleeding ulcers was about 50 Average age of patients who died was about 60 *Hematemesis* from ulcer occurred in a little more than one third of the cases Prognosis was poorer than when melena was present Mortality was highest among gastric ulcer patients death usually being *due to hematemesis (12 of the 15 patients) These patients* also showed the greatest tendency to recurrent hemorrhages especially the women Recurrent hemorrhages during hospitalization occurred in almost one third of the patients (*41% during the first three days and 72% during the first week*) Patients with gastric ulcers were most likely to have recurrences during hospitalization as well as at other times

[Geomedical aspects as well as the influence of a world conflict on the incidence of chronic gastric and duodenal ulcer and on their complications have been a matter of major scientific interest for 35 years In large measure *the experience in Norway has been similar* to that in other European nations Duodenal ulcer is undoubtedly the preponderant universal ulcerative lesion during *periods of great national stress and such* increased incidence should be of etiologic significance Yet during peace time the frequency of duodenal ulcer on the whole is no greater *than* gastric ulcer on the Continent This fact has always intrigued me and there appears to be no satisfactory explanation In the United States the ratio of duodenal ulcer to gastric ulcer at least clinically is 12 1 on

plasma volume 43 cc /kg and whole blood volume 73 cc /kg Sixty one separate tests were made on 23 ulcer patients hospitalized for current or previous bleeding most of whom had received blood transfusions before and/or after initial determinations

Comparison of changes in red counts hemoglobin hematocrit reading and whole blood volume shows that the tests with a few gross discrepancies generally tended in the same direction even if to a different extent In one case slight additional bleeding occurred after the initial loss and 500 cc whole blood was given There was a decrease in erythrocyte count hemoglobin and hematocrit reading but total volume of packed red cells remained unchanged In the 20 days between the first and last tests on another patient with several bleeding episodes who was given 500 cc plasma and 2 500 cc whole blood red cell count increased about 800 000/cu mm hemoglobin 2 5 Gm /100 cc and hematocrit reading rose from 30 to 38 Yet in this interval packed red cell volume decreased from –155 cc to –430 cc equivalent to a loss of about 600 cc whole blood

Hematocrit values had no direct correlation with the red cell mass a value of 34 representing red cell mass deficits from 501 cc in one case to 1 160 cc in another and 35 representing in the first test in one patient an excess of 231 cc and in the second test a deficit of 155 cc Similar discrepancies were found in red count and hemoglobin concentration

While the matter of storage and release of red cells is not universally accepted the effect of hemodilution has been corroborated It is important to recognize the hemodilution effect not mistaking it for continued bleeding Unnecessary blood transfusions with the danger of serum hepatitis and/or overloading of the vascular bed can be avoided if falling hematocrit value is not blindly accepted as evidence of continued bleeding With a single initial blood volume determination extent of hemorrhage can be objectively measured and specific requirements for whole blood plasma or washed red cells estimated In older patients especially those with latent cardiac damage or when whole blood volume is increased above normal replacement of red cell deficit by whole blood may be dangerous

In clinical evaluation the physician needs additional

this *Journal* (p 27) is a report concerning the serious toxic reactions from methimazole the newest of the antithyroid drugs It behooves us not only to be more circumspect in prescribing them but to follow the patients closely for evidence of any unfavorable developments —Ed]

Prognosis of Acute Gastric Ulcer Causing Hemorrhage is discussed by F Avery Jones[1] Number of patients treated for hematemesis or melena from proved or probable peptic ulcer at Central Middlesex Hospital are listed in the table

If x rays failed to demonstrate cause for bleeding two to four weeks after hospitalization lesions were classified as acute Gastroscopy within the first 10 days had often revealed a small or other rapidly healing acute gastric ulcer Of this group all patients who died were over 65 Comparison was made between 37 acute gastric ulcers found gastroscopically but not radiologically and an equal number of chronic ulcers seen radiologically two to four weeks after hospitalization

HEMATEMESIS OR MELENA FROM PROVED OR PROBABLE PEPTIC ULCER

	No	DEATHS
Chronic gastric ulcer	181	35
Duodenal ulcer	367	31
Postoperative groups (previous gastroenterostomies)	76	4
Acute lesion groups	329	8
Others mainly incompletely investigated	67	0
Totals	1 020	78

For every acute case the next chronic case within the same 10 year age group and of like sex was selected and follow up completed There was one death in the acute as against six in the chronic group There was little difference between the two groups so far as severity of bleeding was concerned Greater mortality in the chronic group was attributed to such complications as perforations and to the poor general condition of many patients Follow up showed that with acute ulcer women had a better prognosis than men who showed a striking tendency to later development of chronic peptic ulcer

Repeated Blood Volume Determinations in Bleeding Peptic Ulcer were performed by Sam Kruger Lester Baker and William D Mosiman (V A Hosp Hines Ill) using human serum albumin tagged with I^{131} according to the method of Crispell *et al* Similar previous studies on normal healthy men and based on standard expected weights gave the following results total packed red cell volume 30 cc /kg

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In clinical evaluation the physician needs additional

criteria in regard to continued bleeding which can be more objectively measured by repeated blood volume tests as can the effect of blood transfusions *Repeated use of the Evans* blue (T 1824) dye at short intervals results in inaccuracies because of removal by the reticuloendothelial system Radio active iodinated human serum albumin can be used repeatedly within a short period without inaccuracies and the test itself is easily and safely performed

Combined Service Approach in Treatment of Bleeding Peptic Ulcer *William L Alsobrook Merrill W Schell* and Robert S McCleery[3] (Vanderbilt Univ) report the application of a plan of therapy (Fig 73) in 87 patients who had

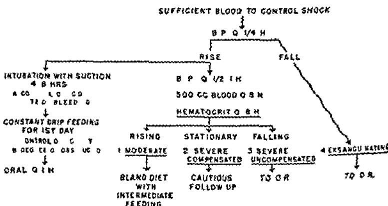


Fig 73 —S h mat c p sentat n of therapy outl ned (Courtesy of Alsob ook W L et l G t ente l gy 21 71 78 May 1952)

immediate surgical consultation on hospitalization Their clinical condition was evaluated and enough whole blood was given to control signs of air hunger and peripheral vascular collapse Intubation was often used to estimate rate of bleeding to control gastric acidity by a high protein drip and to secure information on further bleeding by aspiration

Site of *bleeding was established as soon as practical* A Hampton gastrointestinal series was done during bleeding in 24 Patients with exsanguinating hemorrhage (evidence of peripheral collapse despite rapid replacement therapy) were candidates for immediate surgery After stabilization of *blood* pressure and elimination of air hunger and tachycardia

(3) Gastroenterol gy 21 71 8 M y 1952

response to 500 cc whole blood every eight hours and to the steps outlined in Figure 73 determined whether ultimate management would be medical or surgical

Of 87 patients 4 died 2 of 12 patients operated on to control hemorrhage were among those who died Since control of acidity and estimation of bleeding rate are basic in treatment of hemorrhage 51 were treated with intubation early constant suction and later high protein liquid drip feedings all others had early oral feeding No significant difference in the two series was found but it was suggested that the alleged hazards of intubation are probably insignificant

Only one significant reaction (in an Rh negative patient) was noted in 601 transfusions Seven patients over 40 had exsanguinating hemorrhage three of them died Eight under 40 had serious hemorrhage and one died Mortality for the group was 4 6% The authors believe that use of a combined medical and surgical approach offers promise of still lower future mortality rates

Comparative Study of Effect of Oral and Subcutaneous Banthine® on Gastric Secretion from New Innervated Gastric Pouch in dogs was made by R Armour Forse L J Notkin and D R Webster[4] (McGill Univ) because of the excellent results reported with this drug in control of symptoms of peptic ulcer

Banthine® 50 mg orally caused 20 34% reduction in average volume of daily gastric secretion from the pouches and doses of 100 mg caused 40 50% reduction There was a corresponding reduction in total volume in the insulin and histamine tests A very slight increase in pH and no significant change in pepsin value were also observed

In two dogs 15 mg banthine® subcutaneously caused an 83 87% reduction in secretion volume 5 mg suppressed it almost completely in one 12 kg dog Slight elevation of pH again occurred without significant change in pepsin value Subcutaneously banthine® suppressed gastric secretion for 5½ hours followed by slight increase in volume for 1 2 hours and then a return to control level Thus total volume of gastric secretions was markedly reduced

Ulcer Cancer' *of Stomach* In the literature the consensus is that gastric ulcer predisposes to carcinoma but there is

(4) G [illegible] 21 561 568 A [illegible] 1952

profound disagreement among pathologists about the percentage of ulcers that undergo malignant change Some connection between the two conditions is suggested by a significant relation between chronic ulcerative lesions elsewhere and subsequent malignancy Yet clinical evidence casts doubt on this relation and indicates that malignant change must be more rare than shown by most pathologists figures Also favored sites for carcinoma and ulcer are predominantly different prepyloric region vs lesser curvature Until pathologists in general agree on criteria of *malignant change* and what differentiates ulcer from cancer *de no o* each series must be judged independently

To check the ulcer cancer hypothesis A Davis Beattie and M J Moroney[5] (Leicester Gen l Hosp) attacked the problem by assuming that ulcer and cancer always occur independently in the stomach etiologically and that their occasional intimate association is a matter of chance If the frequency of associated lesions is high etiologic connection would be established By analysis of a statistical model weighting factors in the complex selection mechanism operating along the whole reference chain from differential symptomatology through the practitioner to the surgeon become apparent all of which will influence selection of a potential pathologic specimen Final selection is governed by the surgeon s skill and decision whether to operate and finally to resect When the difference in weighting factors is added to the variability of pathologic criteria it is seen that each pathologist s series must be considered a unique set and that the figures commonly quoted in the literature for the incidence of ulcer cancer are *invalid and illusory*

Reliable information bearing on the causative relationship of ulcer to cancer could be obtained by planned clinical research at large centers Assiduous co operation of all practitioners surrounding these centers would be an essential so that every patient with a suspected lesion would reach the centers at the earliest possible moment before prolonged symptomatic treatment is given Every patient reaching such a center would have to be most carefully investigated and kept under constant review All with proved gastric ulcer would have to be followed in the outpatient department until healing

(5) B t J Ca c 6 215 229 S ptembe 1952

was complete and any failing to respond to treatment together with every patient with a suspected neoplasm would have to be followed vigilantly to either the operating theater or autopsy Research of this type would also require a great volume of routine follow up work and effective co operation of patients However only by such measures will it be possible to detect a secondary neoplasm at or adjacent to the gastric lesion at the critical moment for accurate diagnosis

[This is a searching critical consideration of a subject of perennial interest The authors contend that the figures commonly cited in the literature for the incidence of ulcer cancer are proved invalid and illusory by their method of investigation Their belief that the histopathologic contributions toward the solution of the problem are negligible will be disputed in some quarters One of the most instructive and original features of the article is the proposed method of planned clinical research Obviously the difficulties are great but so is the reward —Ed]

Relation between Benign Ulcer and Carcinoma of Stomach Report of Eight Cases of Malignant Transformation Among the difficulties that have caused confusion regarding the incidence of malignant change in gastric ulcer are (1) carcinomatous change at the edge of peptic ulcer may be confused with reparative changes (2) carcinomas arising in ulcer may have overgrown the original lesion and (3) a chance or independent ulcer may occur anatomically close to carcinoma in the stomach

Certain criteria must be established for histologic determination of the possibility of malignant change in gastric ulcer (1) There should be definite evidence of a chronic gastric ulcer including the characteristic layers of peptic ulceration with a fibrinopurulent exudate a zone of necrosis granulation tissue and a dense fibrous base with loss of muscularis Carcinoma infiltrates and separates the bundles in the muscularis but does not digest them as does peptic ulcer (Figs 74 and 75) In addition there should be vascular changes such as thickening of the vessel walls and formation of thrombi (2) There should be definite evidence of carcinoma such as changes in the staining quality of the nuclei changes in polarity atypical mitotic figures and usually infiltration of the neoplasm beneath the muscularis The carcinoma should begin at the margin of the ulcer and should not be desmoplastic

Using these criteria Charles H Brown Edwin R Fisher and John B Hazard[6] found on routine pathologic examina

(6) G t oen t gy 103 111 S pt mb 1952

profound disagreement among pathologists about the per centage of ulcers that undergo malignant change Some con nection between the two conditions is suggested by a signifi cant relation between chronic ulcerative lesions elsewhere and subsequent malignancy Yet clinical evidence casts doubt on this relation and indicates that malignant change must be more rare than shown by most pathologists figures Also favored sites for carcinoma and ulcer are predominantly different prepyloric region vs lesser curvature Until pathologists in general agree on criteria of malignant change and what dif ferentiates ulcer from cancer *de no o* each series must be judged independently

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Reliable information bearing on the causative relationship of ulcer to cancer could be obtained by planned clinical research at large centers Assiduous co operation of all prac titioners surrounding these centers would be an essential so that every patient with a suspected lesion would reach the centers at the earliest possible moment before prolonged symp tomatic treatment is given Every patient reaching such a center would have to be most carefully investigated and kept under constant review All with proved gastric ulcer would have to be followed in the outpatient department until healing

(5) B t J Ca c 6 215 229 S pt mb 1952

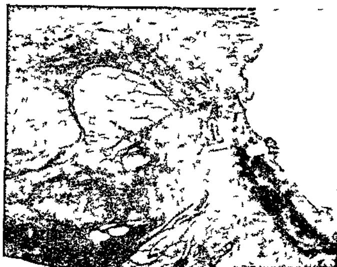
tion eight probable instances of malignant change in benign gastric ulcer These constituted only 1 1% of the benign gastric ulcers observed at Cleveland Clinic during 1945 51 and 1 5% of all gastric carcinomas proved at operation during the same period It is apparent that carcinomatous change can occur in benign gastric ulcer but such an occurrence is rare The main problem for the clinician remains the differential diagnosis of benign and malignant gastric ulcer

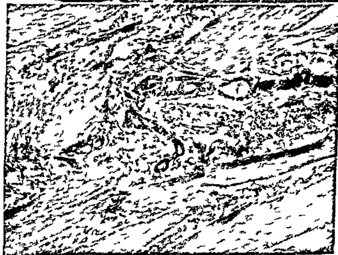
Use of Procaine Hydrochloride by Mouth for Gastrointestinal Disorders has definite benefit as an adjunct to treatment according to Donald C Balfour and George K Wharton (Univ of Southern California) The dysphagia of cardiospasm is usually alleviated except in patients with large saccular dilatation or in the elderly with neuromuscular dysfunction of the esophagus A mixture of concentrated solution of procaine hydrochloride and commercially prepared methyl cellulose solution containing 300 mg procaine/drachm is used The thick solution adheres well to the esophagus One or 2 teaspoonsful is taken before meals or whenever there is distress No food liquid or alkalis should be taken for at least five minutes thereafter The same procedure gives excellent results in esophagitis or hiatal hernia complicated by pain spasm or ulceration Patients with gastritis are relieved by 2 oz of 2% solution three to six times daily

As an adjunct to routine ulcer therapy procaine is especially useful for controlling pain of acute ulcers or treating acutely obstructing ulcers It also relieves vomiting due to gastric or intestinal irritation from medications or vomiting of indefinite nature as in pernicious vomiting of pregnancy x ray treatment and uremic toxemia Many patients with jejunitis after gastric resection have benefited by the direct action of the anesthetic Indirectly there may be reduction of the gastrocolic reflex and alleviation of symptoms in some cases of spastic bowel and ulcerative colitis Toxicity studies and clinical use have shown no contraindication to oral procaine therapy in effective doses

Administration of Fat Emulsion by Mouth, Gastrostomy and Jejunostomy to 90 patients requiring liquid feeding due to obstructive lesions of the mouth esophagus or stomach is reported by Edward M Goldberg Irving F Stein Jr and

(7) G t t l gy 22 257 26 O t be 195





F g 74 —Ul er h w g nt rupt n f mu l w th t ler s e-duc d f om ×8

F g 75 —S m p t nt n F g 4 C m filt t g nd p t g m l b dl n l s f m l d d f m ×70

(C t y f B own C H et l G t t l gy 103 111 S pt mbe 19)

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(7) G t oe t l gy 22 25 62 O t b 1952

Karl A Meyer[8] (Northwestern Univ) All received lipomul* a 40% emulsion of peanut oil with 10% dextrose 2% purified soybean phosphatide and 0 2% synthetic emulsifier (alkylarylpolyether alcohol) 1 000 ml of the emulsion contains 200 mg sodium 250 mg potassium 140 mg chloride 50 mg calcium and 600 mg phosphorus Feedings supplemental to a ward liquid diet were given between meals and before bed time Complete feedings administered slowly throughout the day were prepared by adding 100 Gm of a protein concentrate (Somagen*) 100 mg ascorbic acid 4 Gm sodium chloride and 85 mg iron to 1 000 ml emulsion Somagen* 100 Gm contains 70 Gm milk protein 22 Gm dextrose 150 mg sodium 1 4 Gm potassium 1 2 Gm chloride 1 4 Gm calcium 1 Gm phosphorus 5 mg thiamine 5 mg riboflavin 2 mg pyridoxine 10 mg calcium pantothenate 30 mg nicotinamide 2 mg folic acid 2 Gm liver concentrate and yeast extract from 15 Gm yeast

Of 65 patients with incomplete obstructive lesions fed orally 12 stopped treatment within the first few days because of disagreeable symptoms The other 53 received 300 1 080 ml daily (average 764 ml) 44 patients (83%) gained 1 5 17 lb in 5 30 days (average 5 7 lb in 12 2 days) increased appetite was noted by 21 (40%) and increased strength by 35 (66%) 24 (46%) had no side reactions Among the 81% of patients who continued prolonged feedings 10 (19%) experienced constipation 6 (11%) mild diarrhea and 7 (15%) decreased appetite but only 4 had symptoms severe enough to warrant cessation of treatment Among all 65 patients 28 (43%) experienced nausea and vomiting after which 16 (21%) refused further treatment

The 25 patients with complete obstruction on gastrostomy and jejunostomy feedings were given 250 1 000 ml emulsion daily (average 640 ml) 10 (40%) gained 3 22 lb in 5-49 days (average 9 2 lb in 26 days) Five patients noted an increased appetite and eight increased strength Although 9 had no side reactions 13 had diarrhea 3 nausea and 1 constipation A slow drip over 12 16 hours controlled diarrhea in jejunostomy patients Of 13 patients who failed to gain 12 had far advanced carcinoma the weights of two others could not be recorded

Results were best in patients with benign disease of the

(8) J A M A 150 1665 1667 Dec 27 1952

upper gastrointestinal tract and with malignant disease of the mouth Response in malignant disease of the esophagus and stomach varied depending on the stage of the disease Preoperative feedings in patients with resectable lesions generally gave good results patients with far advanced lesions had only temporary if any benefit Patient intolerance is the chief difficulty in this form of treatment No harmful effects were noted either in clinical or metabolic study or at autopsy among patients who died of malignant disease

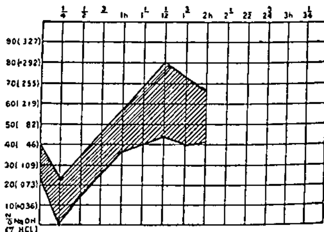
Control of Gastric Acidity No one questions Sippy s statement that gastric hydrochloric acid is the greatest known hindrance to healing of peptic ulcer nor that the high relapse rate would be materially reduced if gastric acidity could be controlled over the 24 hours The inadequacy of most forms of therapy in controlling acidity is well known and the most *effective method of neutralizing stomach contents for long* periods is continuous intragastric milk and alkali drip which presents practical disadvantages

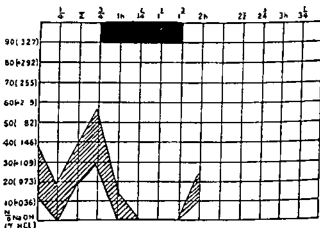
A H Douthwaite and A Batty Shaw[9] (Guy s Hosp London) have tried to adapt the principal end effect of intragastric drip to ambulant patients by prescribing continuous sucking of tablets containing milk solids and alkalis They prepared compressed disks (M tablets) 2 5 cm in diameter and 0 5 cm thick of 40 gr whole milk solids with dextrins and maltose 3 5 gr magnesium trisilicate 2 gr magnesium oxide 2 gr calcium carbonate 0 5 gr magnesium carbonate and oil of peppermint Lodged between gum and cheek they took 20 30 minutes to dissolve and contained about 11 calories

Seven patients with duodenal ulcer and typical high acid curve were given a gruel meal on two consecutive days and *specimens of gastric juice were drawn at 15 minute intervals* During the second meal after the third specimen had been taken M tablets were given Results are shown in Figures 76 and 77

Since swallowing of the saliva stimulated by the action of sucking the pills might have contributed to the successful results a second group of five patients with duodenal ulcer and one with gastric ulcer were studied without the gruel meal over a three hour period the first and third hours being controls *During the second hour they sucked M tablets or boiled* sweets The effect on gastric pH of boiled sweets was so

(9) 1 M J 18(18 J 1 6 195





Fg 76 (top) —S pe mp d g l test m al curv of x p t ents w th duod l l er
Fg 7 (bott m) —S m se G l t t m l d s k g of M t blets d ing p od d c t d hy bl k ct gl
(Co t y of D thw t A H d Sh w A B B t M J 2 180 182 J ly 26 1952

trivial in the first three however that such control studies were abandoned The neutralizing power of M tablets was clearly due to their constituents and not to swallowed saliva

Reduction of gastric acidity with M tablets was far more pronounced and prolonged than by any previous method other than intragastric drip the tablets were pleasant to take and did not cause constipation or diarrhea The method is sug

gested not only for active treatment but to prevent relapse Tablets can replace the extra feedings required by orthodox treatment thereby reducing the likelihood of obesity

The method s chief deficiency is its failure to control night acid Nocturnal secretion which depends on a neural mechanism can be depressed by such drugs as hexamethonium and belladonna which block the vagal ganglions or nerve ends If used in adequate dosage these drugs should provide the *answer to controlling night secretion*

Early Roentgen Diagnosis in Massive Bleeding from Upper Gastrointestinal Tract I Clinical Evaluation of Safety and Reliability of Method in 123 Patients was made by Norman Zamcheck Thomas P Cotter Simon E Hershorn Thomas C Chalmers Max Ritvo and Franklin W White[1] (Harvard Med School) 74 were examined within two and 43 within seven days of hospitalization active bleeding occurred later in the others Most patients were prepared routinely All oral intake was stopped for 8 12 hours before examination Transfusions were given to raise the hematocrit to 28 or higher and additional typed and cross matched blood was available Examination was sometimes postponed because of active bleeding Contraindications to early examination included (1) known diagnosis of duodenal ulcers (2) illness so severe that the procedure was considered unsafe and (3) the patient s inability to co operate Complete roentgen examinations including use of the pressure cone in 43 and omitting cone studies in 47 were performed and 13 patients were examined only in recumbency The extent of examination was not known in 16

Results of the emergency procedure were compared with those of subsequent roentgen gastroscopic and esophagoscopic examinations Tissue was available from 29 operations and 6 autopsies Peptic ulcer was diagnosed 91 times (65 duodenal 26 gastric) esophageal varices 5 times gastric cancer 3 times gastritis 40 times and marginal ulcer twice No satisfactory final diagnosis was made in 12 patients 10 of whom were inadequately studied Initial roentgen diagnosis was confirmed in 92 cases The 14 errors included one gastric and one duodenal ulcer overlooked three gastric ulcers initially interpreted as antral gastritis or duodenal ulcer esophageal varices unsubstantiated in one and overlooked in another

(1) Am J M d 13 713 7 4 D mber 1952

and seven cases of gastritis overlooked Only 3 of the 14 patients had complete initial examinations

Although 12 patients bled severely at some time after examination it was impossible to establish or disprove a causal relationship between the roentgen procedure and bleeding in any No deaths were attributed to the examination It is concluded that emergency gastrointestinal x rays are reliable and that more extensive examinations are possible than was formerly believed Early repetition of roentgen examination is recommended as a valuable and safe adjunct to the initial procedure

[Many physicians are agreed that radiologic examination can be done considerably earlier with safety and profit than was the practice in the past As this report demonstrates an alert radiologist can achieve excellent results in earlier examination of patients with hemorrhage from the upper digestive tract The risk from a complete pressure study as compared with that of the Hampton procedure without pressure is still difficult to evaluate One would tend to favor the latter but more comparative studies are necessary —Ed]

Need for Aggressive Therapy in Massive Upper Gastrointestinal Hemorrhage is emphasized by Burrill B Crohn (New York City) Only massive hemorrhage accompanied by shock and fall of red cell count to 3 000 000 or less and of the hemoglobin level below 7 5 Gm / 100 ml is considered

Conservative management of moderately severe ulcer hemorrhage is satisfactory and is associated with a mean mortality of 6% However at least 10% of patients treated medically die of massive hemorrhage from ulcer After ages 45 50 this figure is materially higher ranging from 15 to 25% The higher death rate has improved little if at all in recent years despite the advent of transfusions blood banks and early liberal feeding The formation of hemorrhage teams (surgeon internist anesthetist and radiologist) has facilitated early diagnosis and has encouraged a direct surgical attack in persons over 50 with repeated rapid hemorrhage The mean mortality rate of early surgery for massive ulcer hemorrhage is 10% Recently with highly elective material and co ordinated staff work this figure has been reduced to 2 6 4 8 and 6% Subtotal gastrectomy with the gastric or duodenal ulcer excised is the operation of choice even in cases with normal findings Subtotal resection in these cases may be curative despite failure to establish the source of bleeding

(2) J A M A 151 6 5 629 F b 21 1953

Reasonably acceptable indications for operation include (1) established diagnosis of ulcer with esophageal varix or other causes of bleeding excluded (2) patient 45 or older and (3) recurrent or continuing massive hemorrhage during the first 72 hours The following factors are indispensable to the therapeutic team (1) a co ordinated clinical and laboratory team including internist surgeon radiologist anesthetist and clinical pathologist (2) a well equipped blood bank and (3) highly developed operating room team work The surgical attack should aim at control of bleeding and definitive cure of the ulcer disease by subtotal gastrectomy

Massive Gastroduodenal Hemorrhage Treatment with Powdered Gelfoam and Buffered Thrombin Solution Preliminary Report is presented by John N McClure Jr[3] (Emory Univ) On hospitalization history taking and physical examination were routine and appropriate fluid or plasma was given intravenously while blood was being cross matched Heavy sedation was maintained with morphine or barbiturates to relieve apprehension or pain Powdered Gelfoam 1 Gm mixed with 250 500 units of thrombin and 50 cc buffer solution was given immediately and every two hours (Buffer solution is prepared by mixing 20 4 Gm disodium phosphate in 1 L distilled water and 1 95 Gm dihydrogen potassium phosphate in 100 cc distilled water These are combined to produce 1 100 cc of M/7 phosphate buffer solution with pH approximately 7 6) Amphojel® 200 cc or other antacid was given alternately every two hours Medication was continued until 24 hours after bleeding stopped or until the patient was prepared for surgery A Meulengracht diet was offered after 6-12 hours or as soon as the patient could take food Cross matched whole blood was given until circulatory equilibrium was established

Of 57 patients so treated 3 died 2 without surgery Three had emergency surgery with one postoperative death There were no fatalities as a result of the first bleeding episode Powdered Gelfoam and buffered thrombin solution seem to be valuable adjuncts to the conservative management of such patients However if response is not prompt operation should be performed early (within 48 hours or sooner)

[Powdered Gelfoam with thrombin appears to be a useful adjunct to the accepted rout ne of med cal management for massive hemorrhage from the upper d gestive tract It is d fficult to evaluate actual effect because of

3) S g y 32 630 637 Octobe 1952

the variable methods of treatment and the greatly improved mortality statistics during the past five years The results by this method probably can be further improved by more effective control of gastric acidity than the proposed antacid regimen offers and by avoidance of any interruption in the treatment routine throughout each 24 hour period It is well known that adequate reduction of the gastric acidity the nocturnal secretion in particular by conventional methods is extremely difficult Use of anti cholinergic agents and the continuous intragastric drip method would maintain the pH of the gastric juice at the desired level thus insuring the clotting activity of the thrombin and the avoidance of peptic digestion of the clot —Ed]

Report of the Committee on Surgical Procedures of the National Committee on Peptic Ulcer of the American Gastro enterological Association.[4] The purpose of this investigation was to appraise critically the results of the various surgical procedures used in the treatment of peptic ulcer and to make a comparative study of gastroenterostomy and vagotomy versus subtotal gastric resection with and without vagotomy in the treatment of duodenal and gastrojejunal ulcer

The records of 4 076 patients with peptic ulcer treated with vagotomy alone or in combination with other surgical pro cedures were studied The data were collected from many sur geons and hospitals by trained statisticians It was found that vagotomy alone for duodenal ulcer produced results signifi cantly inferior to vagotomy plus gastroenterostomy or vagot omy plus gastric resection Vagotomy plus pyloroplasty gave poor results in duodenal ulcer in a relatively small series Gastric retention was the only significant harmful effect of vagotomy Good results following vagotomy could not be cor related with physiologic evidence of the completeness of the vagotomy Vagotomy alone produced definite benefit in cases of gastrojejunal ulcer and this was particularly signifi cant for those gastrojejunal ulcers following gastric resection Results of vagotomy obtained by surgeons from cities report ing less than 50 cases were inferior to those obtained by sur geons from cities reporting more than 50 Neither the opera tive approach (transthoracic or subdiaphragmatic) nor the presence or absence of previous hemorrhage seem to have a definite effect on the results of vagotomy

A study was made of 1 144 cases of subtotal gastric resec tion for duodenal ulcer The data were submitted by the same surgeons who contributed to the vagotomy study Gastric re section was followed by the best results when more than 70%

(4) Gastroenterology 22 295 499 November 1952

of the stomach was removed A history of previous hemor rhage was of serious import so far as good results were con cerned The removal of the ulcer itself had a definitely favor able effect and the dumping syndrome a definitely unfavorable effect on subjective results

Results following partial gastric resection alone were su perior to those following vagotomy with gastroenterostomy and equal to those following gastric resection plus vagotomy for duodenal ulcer except for the higher incidence of hista mine achlorhydria following the latter operation Vagotomy alone may be superior to gastric resection for gastrojejunal ulcer subsequent to previous gastric resection and it is attended by lower mortality

[This is a brief abstract of a report of monographic proportions The difficulties of a statistical study on a nation wide scale of the results of the surgical treatment in such a variable disease as peptic ulcer are fully appreciated The factors giving rise to the inadequacy of a clinical investigation of this nature and scope are summarized in the addendum of this volume which makes interesting reading Notwithstanding these shortcomings we are deeply indebted to the Committee for undertaking this monumental project and to the United States Public Health Service for its financial support —Ed]

Treatment and Prognosis of Acute Perforated Peptic Ulcer The striking fall in mortality of this condition during the last decade (often 20% before 1942) can mainly be credited to improved anesthesia with use of muscle relaxants and anti biotics F Avery Jones and R Doll[5] (Central Middlesex Hos pital) discuss 715 patients hospitalized during 1938 51 and *treated by medical management with gastric aspiration simple* surgical closure or immediate partial gastrectomy

Mortality rate changed little after 1947 in 340 cases in cluding those undiagnosed before death it was 7 9% Of 20 who were not operated on mostly because the condition was not diagnosed or the patient was too ill 17 died In 301 pa tients simple closure was done with 10 deaths (mortality 3 3%) Partial gastrectomy was done in 19 with no deaths The coincidence of hemorrhage and perforation was success fully handled by both simple closure and immediate partial gastrectomy

Seventy four patients with gastric ulcers and a like num ber with duodenal ulcers all with perforation were traced after 2 12 years Ten were not located Eight (11%) of those with gastric ulcers but none with duodenal ulcers died of gas

(5) B t M J 1 12 127 J 17 1953

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(5) B t M J 1 122 127 J 17 1953

tric carcinoma Of all the patients seven (5%) died of peptic ulcer Late prognosis among known survivors was unaffected by age sex or site of ulcer but was influenced by length of history before perforation and by whether or not ulcer had been previously diagnosed (50% of the latter group required further gastric surgery)

No single therapeutic method should be the choice in all cases Medical management does not permit selection of patients for immediate partial gastrectomy after inspection of the ulcer It is contraindicated with bleeding pyloric stenosis or perforation after heavy eating or drinking and in air swallowers It has been practicable and preferable when (1) efficient surgery was not available (2) other associated diseases (recent coronary thrombosis etc) increased surgical risk and (3) perforation occurred at gastroscopy when the stomach is empty

Immediate partial gastrectomy has proved practicable and has given excellent immediate prognosis It is the method of choice for the experienced surgeon when (1) perforation is gastric (although the ulcer may hide an unrecognized carcinoma) (2) there is a history of more than one year of dyspepsia and an ulcer has been previously diagnosed (because many such patients require further surgery if treatment is limited to simple closure) and (3) perforation and hemorrhage occur concomitantly The operation is probably not justified as routine if the ulcer has never previously been diagnosed and if late prognosis with simple closure is reasonably satisfactory Particularly is this true in the absence of prolonged ulcer symptoms when compared with symptoms of the dumping syndrome (should they arise) Surgical closure is highly satisfactory so far as immediate prognosis is concerned It is reasonable to continue its use in the absence of positive indications for either of the other methods

Functional Disorders of Small Bowel after Gastrectomy and Vagotomy Correlation of Radiographic and Kymographic Studies Since partial gastrectomy is now an accepted means of treating penetrating or sclerotic peptic ulcer it is unfortunate that postgastrectomy syndromes can be so incapacitating Yet partial gastrectomy and vagotomy are major mutilations of the alimentary tract and when done in one person it is remarkable that serious complications are not more common Stomal ulcer gastritis of the gastric stump

vomiting due to afferent loop distention and late hypoglycemic manifestations are well recognized postgastrectomy syndromes The postprandial syndrome was formerly believed to be associated with jejunal dilatation but Glazebrook and Welbourn in trying to confirm this found jejunal spasm instead Using kymography and dextrose barium meal radiography A J Glazebrook[6] (Univ of Liverpool) studied 50 patients with abdominal symptoms after partial gastrectomy with or without vagotomy

There appear to be three main types of small intestine dysfunction each of which may cause symptoms (1) intestinal torpor constipation with dull aching abdominal pains postprandially (2) intestinal hurry dumping symptoms after food (especially sweet liquid and bulky meals) frequent bulky pale stools and loss of weight which is sometimes progressive and (3) intestinal spasm constipation colicky abdominal pain (sometimes severe enough to suggest stomal ulcer) with or without dumping symptoms after food Combinations of these motor disorders such as spasm followed by hurry or spasm followed by torpor were more common than any type alone

The author suggests that peptic ulcer or underlying intestinal dysfunction is the cause of both psychic and somatic manifestations of the illness rather than the converse The question is therefore raised as to whether these conditions are the results of the operation or primarily the causes of the illnesses for which the operation was done

Although torpor might be the long term result of successful vagotomy in actual practice the severest examples of intestinal spasm are seen in vagotomized patients Most of these however had vagotomy as a sequel to partial gastrectomy because of persistent postprandial pain stomal ulcer having been suspected but not found at operation Possibly spasm not ulceration caused the pain and vagotomy did nothing to relieve it since vagus blocking agents may afford relief in the syndrome Certainly successful management of torpor hurry and spasm must be based on quite different principles

Partial gastrectomy should be avoided unless there are definite surgical indications—among which failure of medical treatment when the patient is apt to relapse once or twice a year is not included These patients should be strongly urged

(6) Lancet 1 895 899 May 3 19

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The author suggests that peptic ulcer or underlying in testinal dysfunction is the cause of both psychic and somatic manifestations of the illness rather than the converse The question is therefore raised as to whether these conditions are the results of the operation or primarily the causes of the ill nesses for which the operation was done

Although torpor might be the long term result of success ful vagotomy in actual practice the severest examples of in testinal spasm are seen in vagotomized patients Most of these however had vagotomy as a sequel to partial gastrectomy be cause of persistent postprandial pain stomal ulcer having been suspected but not found at operation Possibly spasm not ulceration caused the pain and vagotomy did nothing to re lieve it since vagus blocking agents may afford relief in the syndrome Certainly successful management of torpor hurry and spasm must be based on quite different principles

Partial gastrectomy should be avoided unless there are definite surgical indications—among which failure of med ical treatment when the patient is apt to relapse once or twice a year is not included These patients should be strongly urged

(6) La t 1 895 699 M y 3 19

tric carcinoma Of all the patients seven (5%) died of peptic ulcer Late prognosis among known survivors was unaffected by age sex or site of ulcer but was influenced by length of history before perforation and by whether or not ulcer had been previously diagnosed (50% of the latter group required further gastric surgery)

No single therapeutic method should be the choice in all cases Medical management does not permit selection of patients for immediate partial gastrectomy after inspection of the ulcer It is contraindicated with bleeding pyloric stenosis or perforation after heavy eating or drinking and in air swallowers It has been practicable and preferable when (1) efficient surgery was not available (2) other associated diseases (recent coronary thrombosis etc) increased surgical risk and (3) perforation occurred at gastroscopy when the stomach is empty

Immediate partial gastrectomy has proved practicable and has given excellent immediate prognosis It is the method of choice for the experienced surgeon when (1) perforation is gastric (although the ulcer may hide an unrecognized carcinoma) (2) there is a history of more than one year of dyspepsia and an ulcer has been previously diagnosed (because many such patients require further surgery if treatment is limited to simple closure) and (3) perforation and hemorrhage occur concomitantly The operation is probably not justified as routine if the ulcer has never previously been diagnosed and if late prognosis with simple closure is reasonably satisfactory Particularly is this true in the absence of prolonged ulcer symptoms when compared with symptoms of the dumping syndrome (should they arise) Surgical closure is highly satisfactory so far as immediate prognosis is concerned It is reasonable to continue its use in the absence of positive indications for either of the other methods

Functional Disorders of Small Bowel after Gastrectomy and Vagotomy Correlation of Radiographic and Kymographic Studies Since partial gastrectomy is now an accepted means of treating penetrating or sclerotic peptic ulcer it is unfortunate that postgastrectomy syndromes can be so incapacitating Yet partial gastrectomy and vagotomy are major mutilations of the alimentary tract and when done in one person it is remarkable that serious complications are not more common Stomal ulcer gastritis of the gastric stump

only after a prolonged trial of extensive medical management has proved unsuccessful The authors feel that definitive Bill roth I type gastric resections are associated with less incidence of postprandial distress than are Billroth II procedures

The cause of the syndrome is not completely understood Often mentioned related physiologic and anatomic abnormali ties include (1) jejunitis from irritation of the mucosa by coarse highly seasoned and abnormally hot or cold foods (2) distention of the jejunum by food bulk or secondary to in creased volume of fluid secreted after conversion of sub stances from a hypertonic to an isotonic state (3) excessive sympathetic stimulation due to traction on the esophago cardiac junction by the weight of food in the gastric remnant and efferent and afferent enterostomy loops (4) excessive size of the stomal lumen (5) vagal sympathetic imbalance and (6) combinations of the above

For additional insight into the etiology as well as to extend therapeutic assistance 103 gastric resection patients with post prandial distress were given one or more of the following pharmacologic blocking agents in routine dosage (1) adreno lytic and sympatholytic agents—25 mg priscoline * 50 mg regitine * and 1 mg CCK 179 (2) antispasmodic preparations exerting activity against barium chloride—125 mg pavatrine * 75 mg trasentine * 50 mg 1723 50 mg Win 1670 50 mg Win 5786 and (3) antispasmodic preparations exerting activity against acetylcholine—50 mg banthine * 1/100 gr atropine and 5 mg Win 267C All preparations were administered orally 15 30 minutes before eating

Of the 103 patients treated 46% obtained complete relief after one or more medications 20% partial relief and 34% were not helped The two medications providing complete relief most consistently belonged to the group with predomi nant antispasmodic activity against barium chloride Win 1723 and Win 5786 produced complete relief of symptoms in 35 and 28% of patients but were often accompanied by disagree able side reactions Pavatrine * the most effective drug free from side reactions afforded complete relief in 22% Of the three preparations acting against acetylcholine banthine* and Win 267C produced complete relief in 26 and 21% of patients

to await further therapeutic advances rather than undergo operation Finally when postgastrectomy syndromes develop vagal resection should not be lightly undertaken

[Current methods of gastric surgery are shown up in poor light The author contends that refractory incapacitating and painful sequelae are more common than many surgeons would have us believe More than one third of the patients on his gastric wards were suffering from one or another of the many disturbances that follow gastric resection and/or vagotomy He apparently has not considered the alleged role of jejunitis and the dumping mechanism as well as possible participation in the pathologic physiology he describes

Hirschberg (Gastroenterologia 79 16 1953) and other European observers have attributed to jejunitis the late postcibal distress although it may also occur immediately after eating The hypoglycemic episodes are attributed to it and perhaps a dumping mechanism mediated by the inflamed mucosa Treatment proposed includes prolonged rest in bed and a diet free of cellulose instead of the usual carbohydrate poor rich protein diet for the late manifestations of the dumping syndrome —Ed.]

Treatment of Postprandial Distress Following Gastric Resection In a recent evaluation of 702 patients treated by gastric resection for peptic ulcer Robert F Rauch and Raymond N Bieter[7] (Univ of Minnesota) found postprandial distress in 45% While eating or within 30 minutes thereafter the typical patient experienced profound weakness generalized warmth sudden perspiration drowsiness dizziness palpitations nausea and perhaps crampy gas pains with subsequent passage of a loose watery stool Overeating was often a precipitating cause as were particular foods including milk ice cream and rich deserts Symptoms usually improve with time and are no longer of major concern one year after surgery About 2% of patients however continue to experience incapacitating symptoms and another 17% are troubled to a lesser but still somewhat pronounced degree

Conservative management will usually prove satisfactory Patients should eat a low carbohydrate high fat high protein diet taking less food at lunch and dinner and adding small meals at midmorning midafternoon and bedtime Food must be chewed slowly and liquid omitted with solid food A brief rest before eating and 30 minutes rest immediately after poorly tolerated meals are often beneficial Some form of alcohol before troublesome meals often reduces the incidence and severity of symptoms Surgical correction should be initiated

(7) Gastroenterology 23 347 355 March 1953

Cancer existed or appeared in 10 4% of the total group nine of whom died without an attempt at surgical treatment Cancer was found in 34 (24 3%) of those operated on and proved inoperable in 9 of them The incidence of cancer in 189 patients who had no surgery and in whom medical treatment was unsuccessful was 4 8% Of 31 patients operated on for malignancy whose life span is known 12 (38 7%) lived less than one year 13 (41 9%) three years or more and 7 (22 6%) five or more years after resection

Immediate surgical treatment is recommended for perforating obstructing or bleeding ulcer for chronic ulcer with scarring or an extragastric pocket for ulcer radiologically diagnosed as cancer or strongly suggesting malignancy and for those in which careful medical management and lengthy observation would be difficult Medical management should be reserved for ulcers that are acute small appear least malignant or occur in patients with other conditions contraindicating surgery Difficulties of applying principles of good medical management and the ensuing unsatisfactory results of medical treatment suggest early surgical intervention more often than currently practiced

[A frank though disapp int g report by experienced workers It seems that differential diagnos s and therapeutic results hould have been better considering all the resources available in this large medical center However as pointed out by the authors mo e r gid applicat on of the principles of good management it is believed would have decreased the morbidity and even have prevented the development of gastric cancer Successful differential d agnosis nvolves more than outine case history taking phys cal examinat on and roentgen exam nation A differential diagnosis other than histologic examination of the excised or resected specimen presuppo es con iderat on of the outcome of adequate medical management in hosp tal dur ng which t me successive fecal examinations for occult blood are carried out In addition gastro copic and cytologic examinat ons may also be indicated Perhaps also even the most successful roentgenologist should be more painstak ng Too many ulcers proved to be benign follow g ope ation st ll carry the diagnostic label indeterm nate or probably mal gnant Corrigan and Peterson (Bull Un v of Minnesota Ho p 23 ?43 50 1952) correctly diagno ed roentgenologically as benign 97% of 133 selected ca es They also stated that the decision for resection of benign gastric ulcer should be based on factors other than the fear that all ga tr c ulcers may be malignant It s reasonable to suppose that the prol lem of diagno is and therapy would be solved in large part if all pat ents with gastric ulcer who gravitate to cl n cs and la ge hospitals would co ie under the supervision of a small group of clinicians and surgeons th spec alized skill and experience without p ejud ces or preconce ved ideas and ava ling themselves of current approved methods of diagnos s and therapy —Ed]

as against only 8% of the atropine series None of the adreno lytic preparations proved effective Moreover the use of pris coline* was often associated with severe crampy abdominal pain after meals

Medically Treated Small Gastric Ulcer Five Year Follow up Study of 414 Patients is presented by James C Cain George L Jordan Jr Mandred W Comfort and Howard K. Gray[8] (Mayo Clinic and Found) Surgical treatment was recommended for but refused by 78 patients The other 336 chose medical treatment approved by the consultant for rea sons listed in Table 1

TABLE 1—REASONS THAT PHYSICIAN CONSENTED TO TRIAL OF MEDICAL TREATMENT IN 336 PATIENTS

Re son	Pati n s
Cardiac disease	12
Pulmonary disease	6
Old age and senility	5
Tumors elsewhere in body	2*
Rheumatoid arthritis	1
Alkalosis	1
Cirrhosis	1
Thrombophlebitis	1
Psychoneurosis	1
More urgent surgical measures	1
Ulcer probably benign	305
Total	336

P t ent l ed mo than five y s

TABLE 2—RESULTS ON FOLLOW UP FIVE OR MORE YEARS AFTER START OF TREATMENT

Treatment		
Medical treatment only		
Complete relief	85	20 5
Partial relief	71	17.2
Unimproved	61	14 7
Worse	37*	8 9
Uncertain	20†	4 8
Total	274	66 1
Medical plus surgical treatment	140‡	33 8
Total	414	100 0

F ft n f 37 p t t d d f r lat d a 9 of g t c ca
†All d ed death not due to rel t d
‡Fou su g c l d aths

Results of medical management proved disappointing (Table 2) Only 85 (20 5%) were entirely relieved In 309 varying morbidity continued sometimes for years 140 subse quently underwent surgical treatment

(8) J A M A 150 81 784 Oct 25 195

by repeated efforts at repair and by development of the regenerative nodule In early cirrhosis even though the process is definite clinically and histologically the injection cast of the liver may still be normal (Fig 78) Unlike the normal liver anastomoses of fair size between the portal and hepatic veins are common These uniting small branches of the portal and



Fig 78 —C t f l ly hosis w th f tty h g (lcoh l h) esembl thos t ta d f m orm l l n ev y pect Photog ph w taken w th l ght t ll m t g th p m n f m beh d t m ha t em gu l ty f b h f sel (Cou t y f M J D t l F oc Staff Meet. M y Cl 28 27 3 Ap 1953)

hepatic veins bring about a further diversion of portal blood from the hepatic parenchyma

In one case of hemochromatosis in which a hepatoma had developed the cast revealed that nodules of tumor tissue scattered diffusely throughout the liver were supplied almost entirely by the hepatic arterial system Radicles of the portal vein did not appear to enter the tumor nodules at all Casts of the nonneoplastic portions resembled those of ordinary cirrhosis

LIVER BILIARY TRACT AND PANCREAS

Vasculature of Human Liver Study by Injection Cast Method was performed by Joseph D Mann (Mayo Found) Khalil G Wakim and Archie H Baggenstoss[9]

METHOD—Human livers were removed intact at autopsy The hepatic artery portal vein and hepatic vein were cannulated and each vessel and its ramifications within the liver were flushed with isotonic sodium chloride solution then drained Vinyl acetate in different colors was then injected into each vessel After the plastic hardened tissue specimens were obtained for gross and microscopic studies and the liver was immersed in a concentrated solution of HCl until all tissue was dissolved The resulting plastic cast was studied grossly then dissected for microscopic study

Normal liver casts emphasized the extreme regularity characterizing ramifications of hepatic vessels The hepatic artery twines around the fine branches of the portal vein following it branch for branch to the presinusoid capillaries Between these two vascular trees radicles of the hepatic vein similarly ramify uniformly There were no gross anastomoses between these different vascular trees and interanastomoses within the same vascular system were uncommon Intrahepatic anastomoses between the portal and hepatic veins were not seen However localized areas were often observed in which the portal veins outlined by blue plastic were overlaid by small amounts of red from the hepatic arteries Such overfilling of the portal system occurred whenever the pressure of injection in the hepatic arterial system exceeded that in the venous although connections between the hepatic artery and portal vein were of capillary or precapillary size The hepatic arterial overfilling occurred in a localized zonal fashion with adjacent parts of the liver receiving injection predominantly from the portal vein

Great distortion was present in the vascular pattern of the cirrhotic liver as the regenerating nodules developed All vessels were crowded together in the dense and barren connective tissue septa that separated adjacent nodules The nodules were poorly supplied with vessels of any type These changes are late manifestations of cirrhosis brought about

(9) P oc Staff M t. M yo Cl 28 32 Ap 1953

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Fg 8—C t f l ly h w th f tty h g (l h l b) esembl those tt d f m m l l ry pect Photog ph w tak th l ght t ll m g h p m f m beh d t mph t m gu l ty f b h g f l (Cou t y f M n J D et l P oc Staff Meet M) Cl 8 2 21 Ap 2 19 3)

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Roentgen Hepatography by Injection of Contrast Medium into Aorta Preliminary Report Using a modified technic for abdominal aortography Leo G Rigler Paul C Olfelt and Ronald W Krumbach[1] (Univ of Minnesota) obtained reasonably good roentgen opacification of the liver and spleen The technic differed from that previously used in (1) the use of

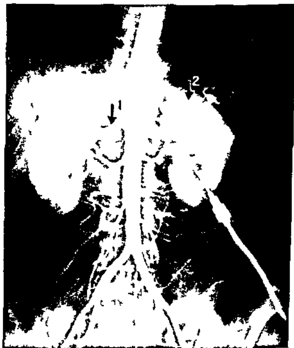


Fig 79 — \ t s m d nmd tly ft j t h w g l t ly l w d ty f l npa d t k j y H jat t y (w 1) jle c a t y (a w) p m t l d l a t s w ll l w \ t b l f h j t t y t d g th gh l (C rt y f R gl L G *et al* Rad logy 60 3 3 367 M h 1953)

70% urokon* as contrast medium (2) the injection of 40 cc within three seconds through a no 16 needle and veterinary syringe (3) the cephalad direction of the needle and (4) the direction of the needle upward to enter the aorta at the 11th thoracic vertebra

X rays were taken immediately before and after injection The increase in density of the liver and spleen was not usually

(1) R d l gy 60 363 36 Ma h 1953

appreciable right after injection (Fig 79) Three to four seconds later however distinct shadows of both liver and spleen of about the same density in normal organs could be observed Eight seconds after injection liver opacification was occasionally even greater At this time the venous return from various abdominal organs was apparent and the portal and splenic veins readily seen Opacification of the portal venous circulation was more striking when there was some obstruction to the flow of contrast medium into the kidneys as in a case of polycystic kidneys In a number of cases of cirrhosis opacification of the liver was greatly reduced Moreover carcinomatous metastases in the liver were revealed as areas of diminished density—a defect within the contrast filled liver substance This lack of contrast in an area of metastasis as well as the general lack of contrast in the cirrhotic liver is predicated upon the compression of the sinusoids which does not permit extension of medium into the liver parenchyma as a whole thereby reducing its opacification The time factor is extremely important in the demonstration of metastases since a lapse of only one second seems to cause disappearance of the contrasting shadows and makes the metastases invisible Films made at least at one second intervals would be a great advantage

[Arteriography and venography are be ng u ed more and more s nce technical advances have increased their af ty and diagnostic value Although many physicians have been reluctant to perforate walls of major arteries Smith Ru h and Evans (J Urol 66 145 1951) reported on over 1 000 ca es without hemorrhage or other mishap The diagnostic advantage of opacification of olid organs like liver pleen and kidneys in certain circumstances is obvious The procedure has al o been helpful in the detection and localization of ntracranial lesions Translumbar aortography according to Creevy *et al* (Bull Univ of M nnesota Hosp 24 413 1953) has proved useful in recognizing renal cysts renal parenchymal neoplasms the r extension and recurrence and in the differentiation of extrinsic and intrins c renal deformities The functions of the vertebral venous circulation were determined by Mellins (1951) by injection of d odrast® into a cannula inserted into the greater saphenous vein at the ankle Venography is also useful in the diagnosis of the Cruveilhier Baumgarten syndrome The technic is simple in this cond t on —Ed]

Analysis of Tests Widely Used in Differential Diagnosis of Jaundice William E Ricketts (Chicago) studied three groups of icteric patients and 20 control subjects The group with hemolytic jaundice comprised 10 patients Of those with parenchymatous jaundice 17 had portal cirrhosis and 21 acute

(2) G st oe t l gy 23 391 402 M b 1953

viral hepatitis In the group with obstructive icterus 17 had cholestatic obstruction of the extrahepatic tract *without septic* infection and 25 had cholangitic obstructive jaundice and a characteristic history of chills fever and pain in the right up per quadrant Direct and total bilirubin cholesterol choles terol ester serum alkaline phosphatase and total protein (Kjel dahl) values albumin globulin ratio prothrombin time intra venous hippuric acid thymol turbidity cephalin cholesterol *flocculation and urobilinogen values in 24 hour urine and feces* collections were measured

In uncomplicated hemolytic jaundice the only abnormal findings were elevated total with normal direct serum bilirubin levels and increased output of fecal urobilinogen Both tests indicated excessive formation and excretion of bilirubin Other test results were not significantly altered

Changes which occurred in obstructive jaundice with or without ascending cholangitis included (1) elevated direct *and total bilirubin levels bile in the urine and increased alka* line phosphatase concentration (2) increased total cholesterol values in 82% with cholangitic jaundice and 37% with chole static jaundice and (3) decreased cholesterol ester ratio in half of both groups In cholestatic jaundice there was no significant change in results of tests of parenchymal function prothrombin time after parenteral administration of vitamin K or hippuric acid excretion *Thymol turbidity and cephalin* cholesterol flocculation values showed little or no change *In cholangitic jaundice parenchymal function* was often but not uniformly altered increase of urinary urobilinogen in 60% hippuric acid values below 0 7 in 33% thymol turbidity above 7 units in 45% and 3-4 plus cephalin cholesterol flocculation value in 18%

In parenchymatous jaundice tests showed similar *results* in portal cirrhosis with icterus and viral hepatitis urinary *urobilinogen levels being most consistently* abnormal Pro thrombin time was the least valuable index (normal values in 73% with viral hepatitis) whereas thymol turbidity and cephalin cholesterol flocculation values were decidedly positive in most jaundiced patients *with portal cirrhosis and viral* hepatitis Hypoproteinemia occurred in both but was *more* pronounced and more common in cirrhosis Tests of regurgi

tation of bile had no value in differential diagnosis as changes occur in both parenchymatous and obstructive jaundice Alka line phosphatase levels above 10 but never above 30 Bodan sky units occurred in one third of patients with parenchym atous jaundice

The various tests used in differential diagnosis should be regarded as expressions of pathologic physiology rather than of particular liver diseases They express no individual morphologic changes but rather the function of the liver as a unit Results were similar in parenchymatous and cholan gitic jaundice and different in biliary tract obstruction with or without ascending cholangitis Similar deviations in test results with jaundice of cirrhosis and hepatitis clearly point *to their relation to diseased parenchyma without relation to* liver fibrosis A disappointing aspect of the study was the lack of sensitivity or value in differential diagnosis in many of the tests including the measure of prothrombin time and the cholesterol cholesterol ester ratio

Laboratory Diagnosis of Liver Disease Co ordinated Use of Histologic and Biochemical Observations Diagnosis of liver disease or jaundice is still more easily made by clinical than by laboratory methods because almost no liver function tests measure basic function and because most hepatic diseases comprise several basic pathologic processes which influence the tests in different ways These basic processes include liver cell degeneration cholestasis (interference with bile flow after formation) inflammation fatty metamorphosis and cirrhosis formation

Hans Popper and Fenton Schaffner[3] (Chicago) discuss a relatively small number of tests selected for their technical simplicity The relation of the tests to histologic features and the factors responsible for such results are described in Table 1 and results of tests and biopsies in a series of patients from Cook County Hospital are given in Table 2

The following etiologic factors cause characteristic vari ations in liver cell degeneration viruses (infectious hepatitis homologous serum jaundice infectious mononucleosis yellow fever) chemical bacterial and endogenous toxins dietary de ficiencies relative deficiencies (due to amino acid antagonists

(3) J A M A 150 1367 1372 Dec 6 1952

TABLE 1—LIVER FUNCTION TESTS WITH LEVELS OF ABNORMAL RESULTS BIOCHEMICAL CAUSES OF ABNORMALITY AND STRUCTURAL ALTERATIONS INDICATED BY ABNORMAL RESULTS*

Test and Abnormal Level	Cause of Abnormality	Structural Alteration Primarily Indicated
Cephalin flocculation higher than plus	Depression of stabilizing albumin and alpha globulin with elevation of precipitating gamma globulins	Liver cell degeneration
Thymol turbidity higher than 5 units †	Depression of stabilizing albumin and elevation of precipitating gamma globulins and lipoproteins (and lipids)	Liver cell degeneration
Zinc sulfate turbidity higher than 12.5 units † and less than 6 units †	Elevation of precipitating gamma globulins and some depression of albumin; Regurgitation of unknown depression factor	Inflammation cirrhosis; Cholestasis
Serum gamma globulin higher than 1.50 gm per 100 ml ‡	Elevation of precipitating gamma globulins	Inflammation cirrhosis
Serum cholesterol higher than 300 mg per 100 ml	Decreased biliary excretion or stimulated production	Cholestasis
Serum cholesterol ester ratio less than 60%	Inability of damaged liver to esterify cholesterol	Liver cell degeneration
Serum alkaline phosphatase higher than 1 Bodansky units §	Faulty excretion of osteogenic intestinal or hepatic phosphatase or increased formation in the liver	Cholestasis

Sulfob n phth l n od m et nt n an accurate meas e f hep t c fun t w s not ut l ed n th s study b u m t f the pat ts we e jau d ced In v ew of th emph g n he e to s um tud s u na y b l rub n d u b l g w e n t e n d d n th d ffe e t l d agn of jaundice

†N n l alu v y ac d ng t sta da ds u ed

‡El v t n abo e 1 25 Gm /100 ml is abn mal For d ff nt al d gno i l v r d s e a h gher b derl e p f bl

§If ad lt el at o ab e 4 Bod n ky u ts is abn n l F de n t at n f ch lestas s h ghe b de l n p efe abl

or depleters) anoxia congestion (due to heart failure) capillary damage (eclampsia) and prolonged biliary obstruction

Jaundice may be associated with obstruction of bile flow overproduction of bilirubin or retention of bilirubin due to

elevated excretion threshold (Fig 80) Intrahepatic cholestasis is treated medically but gives the same laboratory results as jaundice that must be treated surgically, and it is therefore a major diagnostic problem Intrahepatic cholestasis is usually found in viral or toxic hepatitis or cirrhosis with liver cell degeneration

Inflammation is indicated by proliferation of Kupffer cells and infiltration into the parenchyma or portal triads of histio

TABLE 2—PERCENTAGE O CURRENCE OF FUNCTIONAL AND STRUCTURAL ABNORMALITIES IN SERIES OF CASES OF HEPATITIS CIRRHOSIS AND BILIARY OBSTRUCTION

	Acute Hep titis	Ci hosis	Fxt hepati Ob tru ti n
Str tural Ab o m litie	65 Bi psi %	8 Bi p ies %	18 Biopsi %
Li er c ll deg n tio	97 1	95 0	55.6
I flamm ti n	67 6	61 5	38 9
Ch l t is	9 2	11 5	100
F tty metamorph is	1 5	8 2	0
Ci rh si formati n	0	100	0
F ctio al Ab ormalti s	122 D t r mi a ti %	49 Deter mi tions %	Deter min ti s %
C phal n fl cul ti high th n 2 pl s	82 6	74 1	81 9
Thym l t rbidity highe than t	75 5	69 4	64
Zi lf te t bidity higher th n 1 5 its	73 6	83.0	7.8
l e th 6 units	3 5	0 4	2 2
Se um g mm gl bul n high th n 1 50 gi p r 100 ml	57.8	53.5	32 5
S rum hol te l h gh th n 300 mg pe 100 ml	17 0	6 2	38 2
Serum hol t l est le tha 50%	52 0	30.8	58.8
S rum lk lin pho phat e high th n 15 Bod ky its	5 7	6 4	67.0

Th doe n t fl ct th ctual occu ce of f tty li er n ci hos beca ma y f th se p t t h d b d r t eatment t th time f l b p y Thi t true f th h m l d te m t o wh h w d hortly ft dm s

cytes lymphocytes and occasionally plasma cells and segmented leukocytes Proliferation of Kupffer cells and presence of portal unit round cells are associated with increased serum gamma globulin

Fatty metamorphosis is accompanied by surprisingly little functional impairment Thus liver biopsy is better than biochemical methods of diagnosis This condition increases sus

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Zinc sulfate turbidity higher than 12 5 units † and less than 6 units †	Elevation of precipitating gamma globulins and some depression of albumin	Inflammation cirrhosis
	Regurgitation of unknown depression factor	Cholestasis
Serum gamma globulin higher than 1 50 gm per 100 ml ‡	Elevation of precipitating gamma globulins	Inflammation cirrhosis
Serum cholesterol higher than 300 mg per 100 ml	Decreased biliary excretion or stimulated production	Cholestasis
Serum cholesterol ester ratio less than 60%	Inability of damaged liver to esterify cholesterol	Liver cell degeneration
Serum alkaline phosphatase higher than 1 Bodansky units §	Faulty excretion of osteogenic intestinal or hepatic phosphatase or increased formation in the liver	Cholestasis

S lfob m phthal odi m ete t n an accu ate me e f hep t f nct on wa n t t l d n th st dy bec s m t f th p t t wer ja nd ed In w of th emph g n h to er m stud es ur nary b l b n d u b l ge w not c d ed th d ffe ent l d g o of ja nd ce
† N m l al a y cc rd g to ta da ds used
‡ Lle at b 1 25 Gm /100 ml i ab m l F d ff nt al d gn s n l d e e a h gh bo d l n p f at l
§ In ad lt el at o b e 4 B da ky un t l b al F d t at on f chol ta s l gh bo de p ef bl

or depleters) anoxia congestion (due to heart failure) capillary damage (eclampsia) and prolonged biliary obstruction

Jaundice may be associated with obstruction of bile flow overproduction of bilirubin or retention of bilirubin due to

tory test results resemble those in viral hepatitis except that the flocculation tests are often normal

In nutritional or alcoholic cirrhosis great morphologic and functional variations exist Liver cell degeneration and inflammation are as common as in acute hepatitis Cholestasis is not so frequent and fatty metamorphosis is very common but yields to treatment easier than the other features Serum gamma globulin level and zinc turbidity are more often abnormal than in acute hepatitis

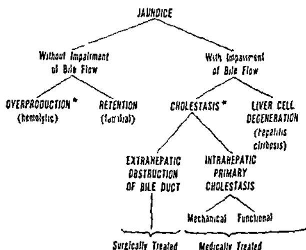
Some cell degeneration occurs early in extrahepatic biliary obstruction but inflammation is usually more apparent histologically than chemically The alkaline phosphatase level and usually the total cholesterol level are high while the serum albumin level and cholesterol ester ratio are low because of cell degeneration Flocculation tests are generally normal even with inflammation since gamma globulin formation is suppressed by bile inhibition of Kupffer cells as shown especially by zinc turbidity Thus low zinc turbidity in jaundice is a valuable indication of obstructive jaundice requiring surgery if cholangiolitic hepatitis can be excluded

In jaundice requiring medical treatment (hepatitis and cirrhosis) cell degeneration usually exceeds cholestasis whereas in jaundice requiring surgical treatment (tumors stones and strictures) the reverse is true The flocculation tests and alkaline phosphatase determination are the most helpful in differentiating them The former are usually abnormal in medically treated jaundice and the latter in surgically treated jaundice However intrahepatic cannot be differentiated from extrahepatic cholestasis by laboratory tests since biopsy shows extrahepatic obstruction only in protracted cases If severe bacterial inflammation complicates extrahepatic biliary obstruction the laboratory tests suggest medical jaundice since the elevated gamma globulin level may produce abnormal results in flocculation tests Here chills and fever with leukocytosis or possibly liver biopsy may clarify the problem

Differentiation of Parenchymal Liver Disease and Mechanical Biliary Obstruction is frequently difficult but obviously needed for proper treatment In an effort to clarify interpretation of the cephalin flocculation thymol turbidity and serum

ceptibility of the liver to injury with acute degenerative changes or leads to fibrosis from (*a*) impaired circulation in sinusoids caused by compression by fat laden cells (*b*) collapse of fat cysts or (*c*) dissection of the lobule by connective tissue originating in the portal triads Whatever the mechanism cirrhosis is the end result Since tests fail to give specific indication of cirrhosis although degree and rate of formation are suggested liver biopsy is the best diagnostic procedure

In viral hepatitis liver cell degeneration is the most striking morphologic and functional change Cephalin flocculation



F g 80 —Type f j und Ast k d t e t t that an be d ff r t ted by l b at y te t (Co t y f I p H and S haff F J A M A 150 136 137 D c 6 195)

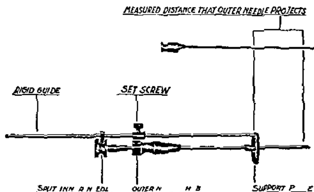
is abnormal thymol turbidity is increased and the cholesterol ester ratio is low Inflammation often occurs in the form of Kupffer cell reaction and infiltration by histiocytes reflected in elevated serum gamma globulin and zinc sulfate turbidity Cholestasis may be present and occasionally serum cholesterol is elevated and alkaline phosphatase level is above 15 Bodansky units Persistent liver cell degeneration is unusual

Toxic hepatitis includes hepatic injury from known or unknown injurious substances It differs from viral hepatitis in that inflammation is less prominent and degeneration more uniform in a given zone fat accumulation may occur Labora

ards of continued observation liver biopsy and exploratory laparotomy

[As repeatedly emphasized the not infrequent coexistence of parenchymatous and obstructive jaundice throws a monkey wrench into our diagnostic procedure The simpler tests outlined are dependable Some workers would also use the more involved technics of determination of urobilinogen content of urine and feces and duodenal drainage in the circumstances With the added diagnostic maneuvers specified by the authors an exploratory laparotomy to clarify the diagnosis should be neces sary less often than formerly —Ed]

Modification of Voegtlin Liver Biopsy Needle for Transthoracic Approach, based on the Vim Silverman biopsy needle is reported by Robert S Nelson[5] The modification permits more rapid adjustment of the stabilizing screw with the needle in liver substance This is done by separating the setscrew and the arm which is fixed to the inner needle (Fig 81) Both



F g 81 —M d fi d V egtl l er b p y n edl (C rt y f Nel on R S G t oent l gy 1 89 290 J e 195)

ride on the rigid guide but the setscrew may be fixed in advance The inner split needle is stabilized requiring no adjustment while the outer needle is in the liver and biopsy need not be delayed

TECHNIC —After anesthesia depth of the liver beneath the chest wall is found by advancing a 22 gauge spinal needle until by feel and motion on breathing it is found to be in liver The attachment is then set so the outer needle projects this distance beyond the support plate the setscrew is lined up on the guide just level with the hub of the outer needle and screwed tight While the patient holds

(5) G t oe t ology 21 289 290 J n 1952

alkaline phosphatase tests Sherman M Mellinkoff Philip A Tumulty and A McGeHee Harvey[4] (Johns Hopkins Univ) reviewed their use in 127 jaundiced patients in each of whom the cause was clearly established by operation autopsy or prolonged observation Extrahepatic biliary obstruction was present in 48 and parenchymal disease in 79

In most patients with parenchymal liver disease cephalin flocculation and thymol turbidity values were elevated and alkaline phosphatase was usually below 15 Bodansky units In obstructive jaundice the thymol and cephalin values were usually normal and the phosphatase was above 15 These tests of altered serum globulin rarely give normal values in active viral hepatitis but in Weil s disease the values are often low even when there is considerable liver damage. In all 14 such cases however the phosphatase value never exceeded 10 4 Bodansky units

Thus if parenchymal disease is suggested clinically and the alkaline phosphatase value is not impressively elevated negative results of serum globulin tests do not exclude parenchymal liver disease Nor does elevation of the cephalin and thymol values eliminate the possibility of extrahepatic biliary obstruction since they will at times be elevated if the obstruction lasts long enough to cause parenchymal damage (18 of 48 cases in this series) Moreover important mistakes will be made if elevated phosphatase level is considered proof of common duct obstruction

Often the phosphatase value will indicate the correct diagnosis if the following points are remembered A high value may result from coincident bone disease It may be high in cirrhosis and some forms of hepatitis With common duct obstruction it may be below 15 units when obstruction is partial or temporary (bilirubin value is not progressively elevated), when coexistent parenchymal liver disease is severe when obstruction is very recent and in a rare case for reasons that are not clear

Continued observation of the patient's course and serial changes in results of these tests will nearly always clarify the diagnosis If not one must then weigh the comparative haz

(4) New England J Med 246 729 733 May 1952

the casual performance of biopsy by the untrained may lead to disaster (3) A needle whose bore is 1 5 1 8 mm seems both safe and satisfactory Larger bores increase the danger of hemorrhage Though the Vim Silverman needle is usually suc cessful many find the specimen from its 1 2 mm bore too small (4) Duodenal intubation should be done whenever there is a possibility of active cholangitis particularly in the pres ence of jaundice and the specimen examined for pus and or ganisms (5) The intercostal rather than subcostal approach is now generally accepted since it permits better control of the needle and avoids piercing other organs which may have enlarged to present in the right upper quadrant (6) Deep pressure over the biopsy site to control bleeding or leakage from the liver wound is recommended for 15 30 minutes (7) Biopsy in the ward rather than operating room avoids danger of bleeding from moving the patient (8) Local application of hemostatic agents does not seem necessary but the patient should remain flat in bed for 6 hours and at rest in bed till the next day and should not be discharged for an additional 24 hours

[The risk of needle biopsy in competent hands with observance of the necessary precautions is negligible This is fortunate because the procedure often establishe a diagnosis which otherwise could not be possible short of more radical procedure Military medical authorities have found that needle biopsy was the most reliable single test for the diagnosis of viral hepatitis —Ed]

Effect of Morphine, Demerol® and Codeine on Serum Amylase Values in Man was investigated by Robert B Pfef fer Hugh C Stephenson Jr and J William Hinton[7] (New York Univ Post Grad Med School)

Method —A total of 56 examinations were performed on 12 fasting patients without history of gastrointestinal disturbance alcoholism or abdominal operations After an initial serum amylase sample was drawn the subject was given 0 015 Gm morphine sul fate 0 010 Gm demerol® or 0 09 Gm codeine phosphate subcutane ously One half hour later 100 units of secretin diluted in isotonic saline was injected intravenously to stimulate pancreatic secretion In another test 100 units of secretin alone was administered as a con trol In a final control test morphine alone was administered Serum amyla e samples were drawn at 2 4 and 6 hours after the initial stimulus Serum values from zero to 335 mg /100 ml were con id ered normal

With morphine secretin studies six patients (50%) had serum amylase values elevated beyond normal In three the

(7) G t oe t l gy 23 482 486 M h 1953

his breath the outer needle already in the chest wall is advanced so the hub is level with the setscrew The inner needle is advanced so that the support holding it to the rigid guide is against the set screw and the outer needle is again advanced with the usual rotary motion sealing off the biopsy specimen The whole apparatus is then removed

This modification makes removal of uniform biopsy specimens by transthoracic approach more certain

Risks of Needle Biopsy of Liver are discussed by Richard Terry[6] (St Bartholomew s Hosp London) on the basis of his own and over 10 000 other biopsies reported since 1939 In this series of 10 600 biopsies the mortality rate was 0 12% (13 deaths) Fatal hemorrhage occurred in 11 patients with a hopeless prognosis One patient died of biliary peritonitis and another of shock the cause of which was not found at autopsy Continued improvement in technic and selection of cases indicates that the rate will probably settle at 0 10% or less

In the present survey 24 significant complications occurred in 7 532 biopsies (0 32%) Significant bleeding resulted in 16 patients Laparotomy was necessary in four transfusion alone in three and expectant treatment in nine It was not possible to assess factors contributing to hemorrhage Biliary peritonitis occurred in seven patients laparotomy being necessary in three Four more cases have been reported elsewhere and obstructive jaundice existed in 10 of the 11 Probably liver biopsy should not be done in cases of definite obstructive jaundice unless secondary deposits or some other feature are being sought Penetration of abdominal viscera though reported at times was not found in this series Tumor seeding in the biopsy track occurred in one case Pneumothorax which appeared five times would probably be found more often if routine chest films were taken but it does not seem to be a significant complication

Among the precautions to be taken the following appear to be the most important (1) Recognized contraindications must be observed e g unresponsive hemorrhagic states (prothrombin levels below 70%) pyogenic infection in the liver inability of patient to co operate absence of superficial liver dulness and moribund senile and anemic patients (2) Since the reported complications usually occurred in the earlier cases while the authors were still inexperienced it seems that

(6) B M J 1 1102 1105 My 1952

the casual performance of biopsy by the untrained may lead to disaster (3) A needle whose bore is 1 5 1 8 mm seems both safe and satisfactory Larger bores increase the danger of hemorrhage Though the Vim Silverman needle is usually successful many find the specimen from its 1 2 mm bore too small (4) Duodenal intubation should be done whenever there is a possibility of active cholangitis particularly in the presence of jaundice and the specimen examined for pus and organisms (5) The intercostal rather than subcostal approach is now generally accepted since it permits better control of the needle and avoids piercing other organs which may have enlarged to present in the right upper quadrant (6) Deep pressure over the biopsy site to control bleeding or leakage from the liver wound is recommended for 15 30 minutes (7) Biopsy in the ward rather than operating room avoids danger of bleeding from moving the patient (8) Local application of hemostatic agents does not seem necessary but the patient should remain flat in bed for 6 hours and at rest in bed till the next day and should not be discharged for an additional 24 hours

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(7) G oe t logy 23 482 486 M b 1953

rise was slight but in three others values rose above 500 mg/100 ml Patients studied with demerol® secretin and codeine secretin showed no significant elevations none had elevated values with secretin or morphine alone The mean values of each test are recorded in the table

Apparently two conditions must be present to produce an elevated serum amylase level after injection of an opiate an obstruction to the pancreatic duct plus the presence of a se creting gland Such conditions exist up to four hours after a patient has eaten if morphine has been used or when there is acute primary or secondary inflammation of the pancreas The interpretation applied to a serum amylase value need not therefore be altered because an analgesic has been used Since

MEAN VALUES OF EACH TEST
WITH AMYLASE VALUES IN MG./100 ML.*

	NO TESTS	2	4	6 H.
M rphi e secr t	12	365 ± 207 3	631 ± 1030 0	579 ± 1043 0
Dem r l-secr tin	11	185 ± 80 3	171 ± 65 5	139 ± 65 7
Codein ec etin	11	166 ± 75 6	168 ± 46 2	130 ± 33 7
Secretin o ly	11	177 ± 29 9	180 ± 38 6	160 ± 55 3
Morph e only	11	169 ± 49 5	163 ± 44 2	154 ± 41 4
8+ Ho s fast ng only	6		1 0 ± 50 9	

* F gu befo ± s th me n val e and aft r ± sta dard de tion of the me n

morphine has greater spasmogenic action and can accentuate the pain of biliary colic demerol® and codeine remain the an algesics of choice in acute pancreatitis

[The reader will recall that Gross and associates had demonstrated an increase in the values for serum amylase and/or lipase in patients with biliary dyskinesia and duodenal ulcer penetrating into the head of the pancreas following hypodermic injection of codeine and morphine Such response could easily lead to a faulty interpretation of the tests If these opiates morphine in particular are used to allay pain of abdominal visceral origin nitroglycerin or its equivalent should be added—Ed.]

Changes in Liver Due to Chronic Passive Congestion The significance of passive congestion in the development of he patic cirrhosis has been long disputed and the following the ories have been advanced (1) that congestion causes increase of connective tissue in the liver (2) that congestion does not produce fibrosis but may favor its development due to other causes (3) that stasis cirrhosis is a rheumatic disease localized primarily in the vessels of the hepatic vein system To learn whether congestion alone can produce increase of

connective tissue in the liver Thomas Castberg[8] (Univ of Copenhagen) studied the livers of patients with clinically verified heart failure manifested by edema and possibly ascites or hydrothorax for at least one month hepatic fibrosis from other causes was excluded Of 205 consecutive patients 84 were selected 39 of them men

Results indicated that congestion contributed to the increase of connective tissue since hepatic fibrosis as well as its severity increased with the duration of congestion The in



F g 82—C t l d l t ti w th f t l port f l ell t bec l P oc d g f m t l bl t t d by fib c ct t b d ee l g th (C t y f Ca tbe g T A ta p th t m b l d 30 343 357 1952)

crease of connective tissue was most pronounced in the lowest portion of the liver where congestion was also most severe However of patients with congestion for two years or longer 70% had an increase of connective tissue and 20% did not It therefore seems unlikely that congestion alone can cause fibrosis Hepatic fibrosis must require a special predisposition or factors other than those so far suggested must coexist

Sites of connective tissue increase in congested livers are characteristic (Fig 82) and differ from those of other forms of

(8) A ta p th et m ob l d 30 343 357 1952

fibrosis in that they are diffuse and found centrally in the lobules Connective tissue increases around the vessels especially those of the hepatic vein system

Morphology and Pathogenesis of Biliary Cirrhosis Eli Moschcowitz[9] reviewed 45 cases of biliary cirrhosis seen at autopsy at Mount Sinai Hospital New York City in 25 years The disease was a consequence of obstruction in 39 cases and of primary chronic idiopathic cholangiolitis in the rest Ex



F g 83—P rtal p c n wh h b le d ct h mplet ly d sappea d f ca cin ma of h pat d t. D at n of j d c 14 m th red ed f m ×183 (Co rte y of M schcow tz E A M A A b P th 54 259 275 S pt mber 1952)

(9) A M A A b P th 54 259 275 S pt mbe 1952

trahepatic obstructions followed carcinoma of the pancreatic head and the biliary ducts in 12 congenital atresia of the biliary tract in 8 cholelithiasis in 7 acquired strictures of the common bile duct in 9 and chronic cholangitis in 3

In the obstructive type the earliest lesions were inflammatory granulomas around the cholangioles which spread into the contiguous portal spaces by angiogenesis There was abundant formation of new bile ducts Later prolongations of the interlobular septa fused forming pseudolobules Simultaneously communications between portal spaces and hepatic and central veins appeared leading to an internal Eck fistula Ultimately normal architecture was completely distorted and the smaller portal spaces and interlobular bile ducts were destroyed (Fig 83) Portal hypertension was sometimes seen with congestive splenomegaly Maturity of the lesions was directly related to duration of jaundice In the primary cholangiolitic type morphology was identical with the final result of extrahepatic obstruction Sometimes there was narrowing or obliteration of smaller ducts indicating widespread intrahepatic obstruction Congestive splenomegaly was usually found

In the pathogenesis of obstructive biliary cirrhosis increased tension within the biliary passages deserves consideration Primary hematogenous cholangitis is extremely rare cholangitis lenta is a purely clinical designation and Hanot s cirrhosis is a syndrome not a morbid entity On morphologic grounds terminal biliary cirrhosis resembles Laennec s cirrhosis except for parenchymal biliary pigment and greater formation of new bile ducts

Cholangiolitic Biliary Cirrhosis (Primary Biliary Cirrhosis) William E Ricketts and Robert W Wissler[1] (Univ of Chicago) discuss nine patients with long standing cholangiolitis and pericholangiolitis but no involvement obstruction or dilatation of the extrahepatic biliary tract lesions were around the smaller bile ducts with secondary fibrosis in these areas (primary biliary cirrhosis) In xanthomatous biliary cirrhosis found in two women without familial history of the disease chronic jaundice hepatomegaly splenomegaly xanthomatosis and pruritus were the outstanding features Edema ascites and collateral abdominal circulation were not

(1) A I t M d 36 1 41 1277 M y 1952

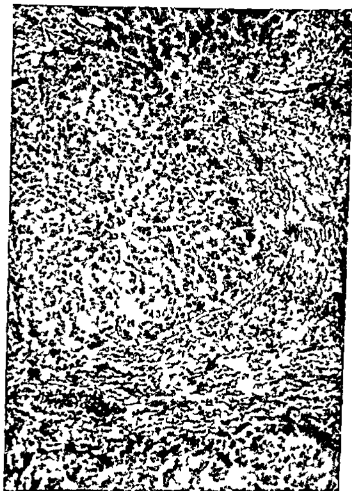
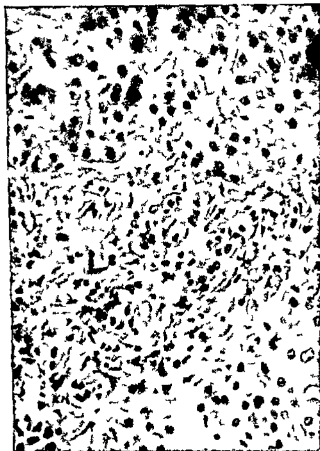


Fig 84—Low pow view f su g al b op y pec m n of l e r m ed about n e yea aft on t of ymptoms a d bo t one y ar aft r po ta eo dec e se of hyp rl pem a j nd a d xa th m L e ow sb w l ge collag n ba d sepa ti g n mal appe g l p e hyma g g an ppea e m lar to po tal c rrhos s (Co rtesy f R ketts W E and W le R W A n. I t Med 36 1241 1277 M y 1952)

noted Neither patient had significant weight loss malnutrition history of chills fever or pain in the right upper quadrant Three males and four females aged 10-64 with non familial nonxanthomatous biliary cirrhosis (Hanot s) had fever jaundice weight loss and pruritus Hepatomegaly was



F g 85 —H gh po ph tom g aph f sam ctio F gu 84 h w g d e ll g nou t w h ly f w fl mmatory ll Sm ll b d t a t ble. P nchym l ll h w mal d p tter d vid f de g t on (C rt y f R ch *tts* W E and W ler R W *Ann Int. Med* 36 1 41 1277 M y 1952)

noted in six initially and appeared in the seventh during ob servation Five had clinical splenomegaly Degree of jaundice varied but always followed a chronic course Increased col lateral abdominal circulation was not observed Edema of the extremities appeared in one undernourished male after a loss

of 45 lb and ascites in one woman after severe blood loss during menstruation

Such evidence of bile regurgitation as elevated direct serum bilirubin total cholesterol and alkaline phosphatase levels was noted in both types of disease but there was little or no change in results of liver function tests Urinary urobilinogen hippuric acid and prothrombin values when measured were not significantly altered but thymol and cephalin cholesterol flocculation were unpredictably abnormal probably due to complex alterations in serum proteins and lipids The persistent high hyperlipemia in xanthomatosis (above 2 000 mg /100 cc) was not found in nonxanthomatous cirrhosis Serum protein electrophoresis in both types showed the peak elevation of the beta globulin fraction characteristic of biliary cirrhosis

Grossly the liver was enlarged with a smooth or slightly nodular surface Histologic study revealed inflammatory changes in and around the smaller intrahepatic bile ducts junction ducts or in the canaliculi between the lobules these were essentially perilobular but sometimes extended into the lobule distorting adjacent cells Small biliary ducts often proliferated and became tortuous and elongated The large ones were unobstructed and collapsed The amount of scarring varied (Fig 84) Generally the liver parenchyma was strikingly preserved and without fatty degenerative or diffuse necrobiotic features (Fig 85)

Posthepatitic and Alcoholic Cirrhosis Clinicopathologic Study of 43 Cases of Each is discussed by Archie H Baggenstoss and Maurice H Stauffer (Mayo Clinic)

Patients with posthepatitic cirrhosis were in general younger (mean age 36) and predominantly female (26 of 43) and jaundice and hepatic insufficiency dominated the clinical picture Patients with alcoholic cirrhosis were in general older (mean age 50) and predominantly male (40 of 43) palpable liver ascites and hemorrhage from varices dominated this clinical picture Hepatic insufficiency was the main cause of death in both groups but hemorrhage and intercurrent infections were more common in the alcoholic than posthepatitic type

Unusually high serum globulin and low blood cholesterol

(2) G stroent rology 22 157 180 O tobe 1952

values were features in some cases of posthepatitic cirrhosis whereas unusually high white cell counts without intercurrent infection were often found in alcoholic cirrhosis Leukopenia was more common in posthepatitic cirrhosis

At autopsy ascites and esophageal varices were more common in alcoholic cirrhosis and liver weight was almost twice that in posthepatitic cirrhosis Outstanding gross features of the liver in posthepatitic cirrhosis included large regenerative

HISTOLOGIC FEATURES IN POSTHEPATITIC AND ALCOHOLIC CIRRHOSIS
(43 CASES OF EACH)

Histologic Features	Type of Cirrhosis: Posthepatitic	Type of Cirrhosis: Alcoholic
Structural pattern	Altered large areas of atrophy especially in left lobe	Altered uniformly hepatic veins eccentric in nodules
Regenerative nodules	Great variation in size larger than 1 cm often far apart*	Uniform size smaller than 0 5 cm closely set
Cell structure	Bizarre forms common	Bizarre forms rare
Infiltration with fat	Slight or none	Usually some may be severe
Alcoholic hyalin	Rare	Usually present
Necrosis	Focal moderate to severe leukocytic reaction is mononuclear	Focal mild to moderate leukocytic reaction is polymorphonuclear
Internodular stroma	Many wide zones	All narrow zones
Connective tissue	Large collapsed reticulum framework	More collagen apparent
Bile ducts	Greatly increased	Moderately increased
Leukocytes	Mostly mononuclear	Mononuclear and polymorphonuclear
Vascular changes		
Venous compression	Large veins compressed*	Severe compression of smaller venules
Inflammation	Often present	Rare

*Th f t d t prtant th g la gup f p th p ttı h [illegible]

nodules and broad zones of atrophy whereas livers in alcoholic cirrhosis were larger granular and often had fatty infiltration Some fat however was found in the posthepatitic type Chief histologic differences are listed in the table

In seven cases of posthepatitic cirrhosis gross and histologic features were similar to those in nonfatty alcoholic cirrhosis and in four cases of alcoholic cirrhosis these features were similar to those in posthepatitic cirrhosis

Metabolic and Clinical Effects of Different Regimens in Patients with Chronic Liver Disease The main therapeutic aims in the care of patients are to regenerate damaged liver

by multiplying parenchymal cells and to alleviate or prevent complications Gordon R Morey Camen R Paynter C Frank Consolazio and Robert M Kark[3] (Univ of Illinois) have at tempted to develop a metabolic mixture which will provide maximal growth and reproduction of hepatic parenchymal cells and repair secondary disturbances rapidly

Frank vitamin B complex deficiency syndromes are rare in cirrhotic or alcoholic patients but protein and caloric de ficiency is common in both They have poor dietary intake and abnormal synthesis and turnover Negative nitrogen balances tissue depletion and water retention are the results

METHOD —Each of four men with hepatic cirrhosis was studied for 126 days divided into seven alternating control and therapeutic periods of 18 days each Dietary sodium was kept below 0 9 Gm and total fluid at 2 5 L /day Calories were provided at basal re quirements plus 100% with 90 mg ascorbic acid 200 mg nicotinic acid 4 8 mg riboflavin 2 7 mg thiamine and 4 9 mg methionine

After the initial control period the first therapeutic period was instituted to the control diet of 2 5 Gm protein/kg /day there was added each day two supplementary intravenous infusions of low salt amino acid hydrolysate containing 60 Gm amino acids in 600 ml distilled water giving a total of 1,200 ml water and 16 Gm nitrogen daily After a second control period several supplements often used for cirrhosis were given methionine choline and cystine three times daily one vitamin B complex capsule and 0 5 10 cc water soluble liver extract intravenously a day During the third thera peutic period 50 Gm salt poor human erum albumin intravenously was added to the supplements given in period 2 The patients were then observed for a final 18 day control period

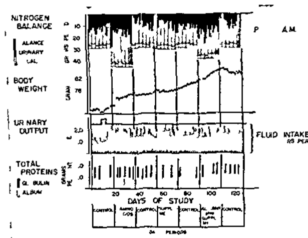
Over all improvement in the four men was striking not only clinically but also in terms of nitrogen retention and liver function as judged by serum cholinesterase activity—the only test that correlated well with clinical findings throughout the study The decidedly positive nitrogen balance indicates the striking capacity for nitrogen retention in all four With 40-50 Gm nitrogen daily when amino acids were given much of the added nitrogen was retained despite a pronounced increase in urinary nitrogen excretion which suggested transitory passage of unchanged amino acids in the urine Urinary cal cium excretion increased with both amino acid and the sup plements perhaps because in patients on low sodium diets the calcium is utilized if sodium is unavailable

Clinically the greatest improvement was noted during and

(3) Metabolism 1 314 339 July 1952

shortly after therapy with the control regimen plus amino acids intravenously (Fig 86) Neither oliguria nor diureses occurred during or after albumin infusions and one patient showed further hepatic impairment during albumin therapy

Although cirrhotic patients improve on 1 0 Gm protein/kg/day comparison of two patients on this level and on 2 5 Gm/kg/day clearly showed the superiority of higher pro-



F g 86—N t og b lan body w ght fl d tak u ry tp t d serum alb min d gl bul l on p t t N tr g n b la tak d tp t g d co d g to Alb gbt h m Th h zontal bas li tak b rt d o se l d wn f m th b se l fecal nd y excr tion th m d f m th tak l p tow d th b l e. If outp t (fece d) doe t d s tak th fi i l l w ll be bel w th bas l f t doe th final l el w ll be bove. Th po t b l d t d by black ea b l w th b l d g t b l by h ded ea bo th bas l (C rte y f M y G R t al Metabol m 1 314-339 J ly 1952)

tein intake in speeding recovery If the amino acids are sodium free do not disturb appetite or produce nausea and if the patient can afford them they seem a valuable adjunct to therapy

[This article should be read in its entirety The efficacy of a diet which supplies 2.5 Gm protein per kilogram of body weight per day and par enteral administrat on of salt poor amino acids over and above the dietary intake of protein is demonstrated. The low salt milk protein preparation u ed was lonalac (Mead Johnson) the low salt meat preparation, Meats for Infants (Swift) Elamine (Interchem cal Corp) was the low sodium lyophylized amino acid brand used —Ed.]

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(3) Metabol am 1 314 339 J ly 1952

liver disease had the highest excretion of both conjugated and unconjugated forms Total estrogen excretion showed a highly significant correlation with bromsulfalein retention and total serum bilirubin values in patients with mild jaundice Two with severe icterus did not show increased estrogen excretion possibly because of decreased production There was no significant correlation with other tests of liver function

Excretion of total estrogens (but not the unconjugated form) in the four patients with advancing or stable gynecomastia was significantly increased over that in patients with regressing or no gynecomastia In those with stable or advancing cutaneous spider nevi excretion of unconjugated estriol was significantly increased

In general high total estrogen excretion was associated with less than average gonadotrophin and 17 ketosteroid excretion Values for both conjugated and unconjugated forms of estriol were increased to a greater extent and more frequently than for estrone or estradiol

In 14 of 17 patients 17 ketosteroid excretion was less than normal It was decreased in the 4 with stable or advancing gynecomastia and in the 6 with testicular atrophy and/or loss of libido compared with patients without these symptoms Gonadotrophin excretion also was significantly decreased in the six with testicular atrophy

Results support the concept of disturbed hormone metabolism as a cause of some of the symptoms of diffuse hepatic disease and suggest that decreased biliary excretion may in part be responsible for the increased urinary excretion of estrogens

Syndrome of Impending Hepatic Coma in Patients with Cirrhosis of Liver Given Certain Nitrogenous Substances Gerald B Phillips Robert Schwartz George J Gabuzda Jr and Charles S Davidson[6] (Harvard Med School) studied the effects of these substances in nine patients with chronic alcoholism and advanced hepatic cirrhosis Four with evidence of fluid retention were fed a constant low sodium diet furnishing 75 Gm protein and about 3 000 calories/day Diets with moderate or no salt restriction providing about 3 000 calories and 100 75 75 and 50 Gm protein daily were given to four others The remaining patient received a regular hospital diet providing daily about 80-100 Gm protein 2 000-2,200 calories and

(6) N w Engl nd J Med. 247 239-246 A g 14 1952

Comparative Effects of Purified and Adequate Diet on Course of Fatty Cirrhosis in the Alcoholic That most chronic alcoholics with fatty cirrhosis improve rapidly when hospital ized and fed a regular hospital diet is well known To clarify the relative importance of food alcohol withdrawal and bed rest in this rapid recovery Gerald B Phillips George J Gabuzda Jr and Charles S Davidson[4] (Harvard Med School) studied three chronic alcoholics with large fatty livers who were given a highly purified diet consisting of 200 Gm glucose and 1 3 Gm sodium chloride dissolved in 1 L water Two consumed about 2 L daily (about 1 600 calories and 2 6 Gm sodium chloride) and the third with frequent nausea and vomiting following ingestion of the solution took only about 1 L After 8 10 days an adequate diet was provided and the study continued for an additional 8 19 days Liver function size and histology were studied at appropriate intervals

None showed significant improvement during the 8 10 days of purified diet with the addition of thiamine alone in one pa tient and thiamine plus multivitamins in another After an ade quate diet for 8-10 days there was improvement in hepatic function in all three with a decrease in hepatic fat in two The third showed a significant decrease in fat after 14 days of the adequate diet These results suggest that the improvement was related to adequate diet and that a subsidiary if any role was played by withdrawal of alcohol and rest in the hospital

Hormone Excretion in Liver Disease Though gyneco mastia cutaneous spider nevi testicular atrophy and loss of libido are frequently found in men with chronic liver disease recent evidence indicates that the role of the human liver in estrogen inactivation is not so important as formerly believed and that the relative inactivity of conjugated estrogens is not apparent when tested at target tissue level F C Dohan E M Richardson L W Bluemle Jr and P Gyorgy[5] (Univ of Pennsylvania) estimated urinary excretion of unconjugated and conjugated estrone estradiol and estriol fractions as well as neutral 17 ketosteroids and gonadotrophins for one or more 3 22 day periods in 5 normal men and 17 with dif fuse hepatic disease

Excretion of total estrogens was increased in 11 patients and of the unconjugated form in 6 Those with most severe

(4) J Clin Invest 31 351 356 Apr l 1952
(5) Ibid pp 481 498 May 1952

between this reaction and impending hepatic coma implies that administration of these substances to patients with cirrhosis may be hazardous

[As noted here grave often irreversible complication of severe hepatic *disease is difficult to predict since no distinctive alterations in laboratory* tests have been described.—Ed.]

Liver Coma, with Particular Reference to Management Michael M Karl Roy A Howell James H Hutchinson and Frank J Catanzaro[7] (Washington Univ) reviewed 58 cases of cirrhosis complicated by hepatic coma and found that all but one of the patients had died and all but one had been in coma at least 24 hours Reports of liver biopsy or autopsy were available in 41 The symptoms objective findings and results of laboratory studies in no way differed from those in patients with severe liver disease without coma Similarly the histologic appearance of hepatic lesions varied widely and often showed no more cellular damage than that noted in biopsy specimens from patients who recovered Since two thirds of the patients lapsed into coma during hospital treatment it seemed desirable to review the treatment used and to search the literature for further suggestions An attempt was made to select all forms of therapy previously discussed that seemed of real or theoretical value

When nutrition is so important as a therapeutic measure the dangers of inducing bleeding or aspiration pneumonia by tube feedings do not seem real enough to offset their obvious advantage Such feedings are given by slow constant drip One of three special mixtures the choice depending on the total number of calories and the sodium content desired has been used Mixture 1 has 1 950 calories in 1 300 cc with 104 Gm protein 46 Gm fat 280 Gm carbohydrate and 1 300 mg sodium Contents are 200 Gm powdered skimmed milk 20 Gm cocoa 20 Gm sugar and 1 qt whole milk Mixture 2 has 1 850 calories in 1 300 cc with 88 Gm protein 100 mg fat 150 Gm carbohydrate and 527 mg sodium Contents are 200 Gm lonalac 20 Gm cocoa 20 Gm sugar and 1 qt whole milk Mixture 3 has 1 172 calories in 1 000 cc with 56 Gm protein 60 Gm fat 102 Gm carbohydrate and 27 mg sodium Contents are 200 Gm lonalac 20 Gm cocoa 20 Gm sugar and 1 qt water Parenteral administration of vitamin supplements (such as betasynplex® with vitamin C ascorbin B or betalak)

(7) A M A Arch. Int Med. 91 159 176 February 1953

unrestricted amounts of salt except during a period of high protein administration Four oral medications were used Ammonium potassium cation exchange resin was given in aqueous suspension ammonium chloride as 0 3 Gm nonenteric coated tablets and diammonium citrate chemically pure as 1 Gm capsules Urea was dissolved in water or fruit juices and given as a 50% solution

The untoward reaction to these substances was similar in all five patients in whom it developed and consisted of mental disturbances a flapping tremor and EEG changes Similar signs of hepatic coma were not known to have occurred previously except in one patient The mental change appeared as clouded consciousness confusion and grossly inappropriate behavior No patient became comatose The tremor was absent at rest developed on active maintenance of posture and consisted of an irregular coarse flexion extension movement at the metacarpophalangeal and wrist joints and when more severe at the elbows and shoulders The EEG changes were chiefly bursts of bilaterally synchronous slow waves in the frontal regions These findings all reversed within a day or two after withdrawal of medication with no residuals

In two patients the reaction resulted from ammonium containing resin and orally administered ammonium chloride A third patient showed the reaction with diammonium citrate and urea but not with high dietary protein intake Increased dietary protein caused it in two additional patients

The mechanism of the reaction is not clear Because three of the substances administered contained ammonium and the urea and protein administered may have been transformed into ammonium by intestinal bacteria this ion was studied as the possible cause Correlation between blood ammonia concentrations and the abnormal signs observed was not consistent enough to establish a relation

Alterations in serum pH and sodium potassium and carbon dioxide concentrations and in blood nonprotein nitrogen levels were also considered possible causes but serial measurements failed to reveal any correlation with the reactions One patient who was acidotic during the reaction to ammonium chloride did not show the characteristic abnormal signs when made acidotic to a similar degree with calcium chloride

Though the untoward reaction was reversible in every instance without clinical residua the pronounced resemblance

which would influence sedimentation rates were excluded Fifteen patients had chronic cholecystitis Symptoms if present were mild being limited to tenderness in the right upper quadrant in 67% White blood cell counts were elevated in 20% and sedimentation rates ranged from 3 to 21 (average 13) This group demonstrated that chronic gallbladder disease does not produce significant alterations in either white cell count or sedimentation rate

Subsidence of symptoms and decrease in abdominal findings were noted early in 84% of 45 patients with a pathologic diagnosis of acute cholecystitis *Normal or falling white cell* counts in 77% indicated subsiding disease Evaluation therefore based on clinical findings and leukocyte counts alone was inadequate Notable through the series however were persistently high or rising sedimentation rates Of 19 patients studied by serial sedimentation rates and white cell counts 78 9% had rising rates 21 1% had persistently elevated rates and all coincidentally had falling white cell counts

A rising or persistently elevated sedimentation rate was the only finding preoperatively that appeared consistently to correlate with the severity of the pathologic process in the gallbladder

Timing in Surgical Treatment of Acute Cholecystitis Paul T DeCamp Alton Ochsner Thomas G Baffes Huldah Bancroft and William Bendel[9] analyzed 468 consecutive cases observed at Charity Hospital New Orleans during 11 years Six gallbladders were examined at autopsy only and the others were examined at operation Patients ranged in age from 12 to 87 (mean 50) and the ratio of females to males was 4 1 In proportion to hospital admissions case incidence was almost twice as great among whites as among nonwhites the incidence among nonwhite males being particularly low Only 21% had no previous symptoms and 30% had had symptoms over three years The acute attack was usually dramatic pain and tenderness in the right hypochondrium were almost universal Rigidity and a palpable mass were each present in 49% and jaundice in 23% A leukocyte count of over 10 000 and a temperature of 99 6 F or higher occurred in 76 and 74% respectively Pathologic observations included cholelithiasis 92 4% gangrene 24% empyema 14% choledocholithiasis

(9) A n S g 135 734-750 M y 1952

which contain several times the daily requirements may be added to each feeding or each liter of fluid When adequate carbohydrate intake is assured by tube feedings parenteral administration of glucose may be superfluous Several patients in this series who had not had paracenteses or mercurial diuretics showed a sharp drop in blood electrolyte levels after the intake of large quantities of glucose in water probably due to electrolyte dilution on the basis of water intoxication

When tube feedings are not possible nutritional requirements representing 100 200 Gm protein and 300-400 Gm carbohydrate may be supplied by parenteral feedings of amino acids and glucose The concentration of glucose and amount of salt will be determined by the total fluid and electrolyte requirements according to the general principles followed in the treatment of any disease Factors in hepatic coma which may influence these principles include urinary output fever vomiting the use of paracenteses or diuretics and bleeding

The administration of 1 Gm aureomycin daily by stomach tube offers broad coverage for infections and may help to prevent hepatic necrosis When aureomycin is used or when the prothrombin time is low vitamin K should be given parenterally in 72 mg doses although the response may not be gratifying Intravenous administration of crude liver extract in gradually increasing doses to 20 cc daily or more diluted to 1 000 cc is apparently of value Ordinary crude liver extract prepared for intramuscular administration does not seem to cause reactions oftener than preparations for intravenous use Anemia may be corrected by blood transfusions or administration of washed red cells according to fluid requirements output and cardiac state Massive doses of vitamin B_{12} may be of value in macrocytic anemia Whenever possible ascites should be controlled by 200 600 mg sodium intake and the use of crude liver extract and mercurial diuretics rather than by paracenteses The dangers of water intoxication hyponatremia and hypokalemia should be avoided by careful control of fluid and electrolyte balance

Sedimentation Rate in Acute Cholecystitis. Using Wintrobe s method Thomas H Hewlett[8] (U S Army Hosp Camp Breckinridge Ky) studied 60 patients with a diagnosis of cholecystitis Patients with coincidental diseases

(8) U S Armed F ces M J 3 1267 1278 September 1952

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(9) An S g 135 734 750 M y 1952

11 5% generalized peritonitis 5 6% and adenocarcinoma 1 3% Incidence of gangrene and empyema was highest in patients for whom conservative treatment was attempted but abandoned because of progressive symptoms

Of the entire series 289 patients (61 7%) were operated on promptly and 183 (37%) had delayed operation In 125 initial conservative treatment was successful, in 48 the disease progressed despite medical treatment and required emergency operation Postoperative morbidity was not significantly higher after prompt than after delayed surgery

There were 39 deaths a mortality rate of 8 3% for all cases and 7 5% for all operative cases Rates were significantly affected by age and the severity of the acute attack Mortality was 6% for 285 patients treated less than 4 days after onset 12 3% for 138 treated 4-10 days after onset and 11 1% for 45 treated over 10 days after onset The respective rates adjusted for age sex and severity of disease were 6 2 10 3 and 14 1% The adjusted rate for all patients treated four or more days after onset was 11 1% Serious complications tended to occur if surgery was delayed analysis of deaths revealed that 50% might have been prevented by earlier operation Attempted initial conservative management was usually successful in patients seen 4 10 days after onset but often failed in those seen either within 72 hours or more than 10 days after onset Death seemed more often due to the advanced stage of disease which demanded immediate operation rather than to ill advised prompt operation on patients who might have been managed medically Prompt surgical treatment as soon as the patient can be properly prepared seems to be the treatment of choice except in some patients first seen 4-10 days after onset

[The timing advocated should meet with general approval Obviously no standard method of treatment is feasible In the last analysis the surgeon usually will be guided in the individual case by his skill and judgment based on past experiences As 70-80% of the patients with acute cholecystitis have had previous symptoms referable to cholecystic disease it is apparent that this serious complication could have been avoided by operation earlier in the course of the disease Another cause for concern is the fact that perforation occurs in about 11% of patients with actual acute cholecystitis The practitioner is also concerned about the possibility of injury to the extrahepatic ducts which is a real tragedy and still occurs too frequently Only a minority of patients are operated on by highly experienced and skilled surgeons general practitioners and occasional operators attend to the majority The danger is in removing instead of draining the gallbladder especially if the anatomic features are

not distinct, and it is surprising to know that many operators feel it necessary to remove the gallbladder in every case of acute cholecystitis When serum amylase determinations are done routinely following severe biliary colic it is surprising how often the pancreas is found to be acutely involved Many surgeons feel that this is justification for delaying operation until the inflammation has subsided —Ed]

Effect of Complete Vagisection and Vagal Stimulation on Pancreatic Secretion in Man Using five young healthy controls and eight patients with complete vagotomies from previous esophagogastrectomy with esophagogastric anastomosis David A Dreiling Leonard J Druckerman and Franklin Hollander[1] (Mount Sinai Hosp New York City) performed the secretin and insulin tests

METHOD —Following a 12 hour fast the subjects were intubated and gastric and duodenal secretions were collected by continuous suction After resting specimens were obtained 1 unit of secretin/kg body weight was injected intravenously and specimens were aspirated for four 20 minute periods After a 20 minute resting period 20 units of regular insulin was injected intravenously Drainages were continued for four more 20 minute periods and blood samples for sugar assay were taken before and 30 60 and 90 minutes after insulin injection Measurements were made of volume pH and free and combined acidities for gastric secretion and of volume bicarbonate concentration icterus index and amylase concentration for duodenal secretion Only blood sugar values of 50 mg /100 cc or less were considered to indicate sufficient hypoglycemia to assure stimulation of the vagal center

In the controls hypoglycemic vagal stimulation produced pancreatic fluid with low total volume and high amylase content compared with secretin response but with no increase in bicarbonate concentration Marked increase in enzyme secretion was the main effect In vagotomized patients hypoglycemia did not stimulate pancreatic secretion but response to secretin was entirely normal Apparently vagotomy did not seriously interfere with digestion through its effect on external pancreatic secretion since the hormonal mechanism and local nervous reflexes seem to be more significant than the vagal mechanism From this standpoint vagotomy for peptic ulcer need not be proscribed Digestive disturbances e g diarrhea and steatorrhea in the postvagotomy state are not due to pancreatic insufficiency

It may be possible to estimate the completeness of vagotomy under special circumstances by determining pancreatic secretion after insulin hypoglycemia since with complete vag

(1) G[illegible] 20 578 586 Ap 1 1952

otomy the amylase output characteristic of vagal stimulation should be entirely absent This would be useful when the insulin acidity test yields equivocal results or when anacidity develops in postgastrectomy vagotomy patients as a result of the operation

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THE INTESTINAL TRACT

Critical Levels of Mineral Oil Affecting Absorption of Vitamin A were studied by Frederick Steigmann Hans Popper Hattie Dymewicz and Irene Maxwell (Univ of Illinois) Patients with no gastrointestinal liver renal pulmonary or cardiovascular disease were for several weeks put on a standard diet containing 1 500 3 000 I U of vitamin A (mostly carotene) Plasma vitamin A and carotenoid values were determined twice weekly using the Coleman spectrophotometer The study included 115 experimental periods of three to four weeks each in 66 patients

On diets containing 2 500 I U of vitamin A potency the average vitamin A levels remained constant whereas on diets with 1 500 I U average levels fell significantly and on diets containing 3 000 I U levels tended to rise

When the 2 500 I U vitamin A diet was used 30 cc mineral oil mixed in the noon meal (6 8%) decreased plasma vitamin A levels whereas 5 cc (1 1%) was without effect Administered three times daily in meals 10 cc mineral oil caused a marked drop of the vitamin A level 5 cc a moderate drop and 2 5 cc none On a diet containing 3 000 I U of vitamin A 30 cc mineral oil with the meal also reduced the plasma vitamin A level but 30 cc given at bedtime independent of meals was without effect

Present Day Problems in Appendicitis from Internist's Viewpoint are discussed by Lucian A Smith[3] Three points deserve emphasis (1) difficulties in diagnosis of a condition so common (2) the pain mechanism peculiar to acute appendicitis and (3) the change in treatment of complications of the disease

Diagnostic difficulties are so common that appendicitis is unusual when it is typical Gastroenteritis mesenteric lym

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(2) Gastroe t (l gy 20 587 594 Ap 1 195
(3) Proc Staff M t M yo Cl n 8 1 5 J u y 1953

phadenitis right ureteral stone right adnexal disease and gall bladder disease are relatively common differential possibilities Other less common complications include amebic cecitis followed by fecalith appendicitis acute shigellosis with simultaneous obstructive fecalith appendicitis acute salmonellosis ligneous appendicitis and cecitis simulating carcinoma of the cecum and infarction of omental or epiploic tags

The usual pain involves two pathways First aching cramping or hunger pain poorly localized in the periumbilical or epigastric region appears accompanied by loss of appetite nausea and finally vomiting This pain is mediated by the splanchnic or visceral pathways Several hours later the pain localizes in the right lower quadrant where it traverses the parietal or somatic pain fibers These fibers run in the segmental nerves and provide an accurate means of determining the location of the inflammatory process

In acute retrocecal appendicitis the visceral pain phase is usually short and is followed by early localization in the flank Since the parietal peritoneum is quickly involved and is innervated by somatic pathways the pain is similar to early pain in diverticulitis Moreover the appendix does not have to lie against the right ureter to give rise to pain referred to the right groin labium testis or upper thigh Such pain results from involvement of the neural pathways of the 12th dorsal and 1st lumbar segments When the parietal peritoneum becomes involved in cases of acute retrocecal appendicitis the pain elicited on rebound is located in the right flank rather than in the right lower quadrant Appendical colic is the result of splanchnic pain and probably represents an attempt of the appendix to expel the fecalith Many authors believe appendical fecaliths indicate previous disease of the appendix

Treatment has been greatly improved by better diagnosis better control of electrolyte balance improved surgical measures including intestinal decompression and use of new antibiotics Treatment of peritonitis with aureomycin penicillin combined with streptomycin or terramycin have all been effective Broad spectrum drugs as a rule are preferred because of their effectiveness in control of organisms which commonly affect the colon Antibiotic therapy however should be used

to supplement but not to supplant sound surgical technic in the management of complications

[To many a consideration of appendicitis seems academic However problems in diagnosis are a daily experience When the acute disease progresses to one or more of its complications serious illness and even death still occur In this ever decreasing group is early diagnosis particularly important Among the various conditions that may simulate an inflamed appendix is malignant disease of the cecum One large clinic reported that 15% of patients with this disease had previously had the appendix removed —Ed]

Simplified Duodenal Intubation with New Polyethylene Tube with specially designed metal bucket (Fig 87) is described by Milton J Matzner Harold Zarowitz Peter Wedeen and George C Cohn[4] (Jewish Hosp Brooklyn)

APPARATUS —The bucket is olive shaped weighs 67 Gm and is

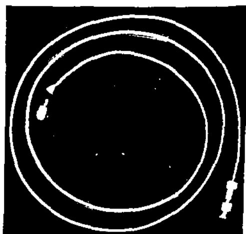


Fig 87 —P ly thyl e g t d ode l t b w th tw secto s f b k t d sen g d (C t y f M t M J *t al* G t oe t rol gy 21 419 425 J ly 1952)

3¼ in long with maximal diameter of ⅜ in It has one central and four lateral openings for drainage The polyethylene tube is 52 in long with a 1 4 mm inside and a 1 9 mm outside diameter To facilitate its introduction and prevent coiling in the patient s mouth a 12 in plastic guide tube is threaded over the finer gastroduodenal tube A coupler is secured to the proximal end by a flange for use with a Luer Lok syringe for instillation or aspiration

With the patient sitting the tubes and bucket are passed over the tongue into the oropharynx after which the polyethylene tube is rapidly threaded through the guide tube held

(4) G stroe te ology 21 419 425 J ly 1952

in its original position The patient is encouraged to keep swal lowing during passage of the tube until about 34 in of the inner tube is passed he then lies on his right side until intuba tion is completed

The procedure is performed in the morning with patients in the fasting state Position of the tube is checked by the various technics recommended by Bockus or by x ray localiza tion The authors had only two failures in 36 duodenal intuba tions including one in a child of 14 months

[The very low failure of succe sful intubation with the authors polyethylene tube is a tribute to the kill with which the patients were managed The weight and shape of the metal bucket is probably not the answer The use of a light small caliber polyethylene tube is certainly welcomed by the patients being intubated However wl en one considers that successful intubation depends on gastric tonus and peristaltic activ ity and that there is no impairment of these physiologic proces es in any of the patients intubated it is difficult to attribute too mi ch to the use of the pla tic tubes The lightness of the plast c tube only would become a factor if the weighted bucket were required to pull the tube through the pylorus Such is not the case however As re emphasized by Cantor tubes are successfully passed becau e of the peristaltic acti ty of the bowel which cau es all intestinal content including intragastric tubes to be propelled caudal ward —Ed]

Jejunal Diverticulosis with Hemorrhage A P Waterson[5] (London Hosp) states that massive gastrointestinal hemor rhage presents both diagnostic and therapeutic problems Though rare jejunal diverticulosis should be borne in mind as a possible cause

Man 59 was hospitalized in coma with gross pallor of skin and mucosa weak pulse and blood pres ure 100/65 mm Hg For about five months he had complained of increa ing las itude and central abdominal discomfort de cribed as a pulling on the navel Three months previously a hydrocele on the right side had been tapped Ten days before admi ion he vomited once and soon afterward passed a copious black tarry tool Next day he passed ome bright red blood with clots stools on subsequent days were tarry Sig moidoscopy four days before admission was unsuccessful because of a loaded bowel Ten hours before admis ion hemorrhage of bright red blood began per rectum and continued Other hi tory was not ignificant

He was given 1 pt pla ma immediately followed by 5 pt blood Next day he wa con cious but confu ed blood pre sure rose to 170/100 Three days after adm sion he was better with hemo globin value 10 5 Gm /100 ml Sigmoidoscopy to 22 cm on the eighth day revealed no abnormality Two days later he felt faint and pa sed two tarry tool That evening he became pale and shocked with sighing re piration blood pressure fell to 90/60 He was given

(5) Lancet 2 1033 1034 N 9 1952

3 pt blood Next morning he passed about 3 pt bright red blood including some clots A third transfusion of 5 pt blood was started. That afternoon he vomited 10 oz dark brown coffee ground material however by midnight he was conscious and rational Two days later he received another 3 pt blood and in two days the hemoglobin value was 7 6 Gm /100 ml That afternoon he suddenly complained of a feeling of impending death became pale and sweated profusely pulse became weak and rapid and blood pressure fell to 80/60 He improved after receiving another 4 pt blood but passed a small black stool that evening Next day his general condition was improved and blood pressure had risen to 160/95 It was decided to perform exploratory laparotomy with a view possibly to emergency partial gastrectomy Penicillin 100 000 units twice daily was started Bleeding and clotting time were normal

At operation no abnormality was found in the stomach or duodendum There were numerous saccular diverticula 1 5 cm in diameter in the first 3-4 ft small intestine below the duodenojejunal flexure on the mesenteric border with evidence of recent fibrinous peritonitis over many of them The part most affected was immediately below the duodenojejunal flexure here one diverticulum contained a concretion which could be extruded easily into the bowel lumen and passed without difficulty The small intestine contained blood only in the lowest 1 2 ft of the ileum Cecum and colon contained much dark red blood but were otherwise normal as were liver and spleen The diverticulum containing the enterolith was considered the source of bleeding Resection of the affected bowel segment was the treatment of choice but because of the patient s age and general condition the abdomen was closed without drainage About three weeks after operation he was discharged free from abdominal pain He had continued well for four years but recurrence is considered possible

[One should suspect the small bowel as the source of single or recurrent episodes of melena in the absence of symptoms or signs of peptic ulcer or other lesions in stomach or duodenum Lesions like benign tumor and Meckel s diverticulum in the absence of complications like obstruction often escape radiologic detection so that exploration in principle may be justifiable Similar cases have been reported by others Thus is added another entity to the growing list of conditions that may be obscure causes of hemorrhage —Ed]

Latent Steatorrhea Douglas G Cameron C H Bensley and Phyllis Wood[6] (McGill Univ) observed eight cases in two years Five men and three women aged 18-57 presented one or more of the following conditions tetany frank osteomalacia unexplained megalocytic anemia and iron deficiency

(6) Ann. Int M d 37 553 558 Sept mber 195

Symptoms had been present 2-48 months average 21 months None of the patients had lived in the tropics or had a clear history of celiac disease in childhood Six denied gastrointestinal symptoms of any kind Two gave a history of occasional watery diarrhea but did not recall that stools had ever been pale bulky frothy or especially offensive Moreover inspection of feces did not reveal characteristics of idiopathic steatorrhea in any case Fat balance studies were made over 12 days in six and over 8 days in two cases For three days before and throughout the study patients received a daily diet containing 75 Gm fat (70 Gm in milk butter and eggs) 60 Gm protein and 360 Gm carbohydrate Daily fecal fat ranged from 8 to 27 Gm representing 11 36% of intake and indicating steatorrhea in every case

All patients responded to routine treatment Megalocytic anemia was corrected by folic acid orally or liver extract parenterally iron deficiency by saccharated iron oxide intravenously tetany and osteomalacia by calcium lactate and vitamin D orally and prothrombin deficiency by vitamin K Multivitamin preparation was prescribed to relieve any deficiencies not clinically apparent

When no other cause is apparent the protean manifestations of idiopathic steatorrhea should suggest the diagnosis even though bowel disturbances have never been present

Malabsorption Syndrome is the term preferred by E G Saint and S Weiden[7] (Royal Melbourne Hosp) to describe all cases of sprue celiac disease idiopathic steatorrhea and steatorrhea complicating disease of the intestinal and mesenteric lymph nodes Four cases are presented two of which were idiopathic. In the third case malabsorption was secondary to gastrocolic fistula and cure followed operation In the fourth it was secondary to reticulosis of the mesenteric lymph nodes Nitrogen mustard produced remarkable clinical improvement

The standard oral glucose tolerance test an oral glycine test and a butter fat tolerance test were used for evaluation in addition to the quantitative van den Bergh and cephalin

(7) A t l A Med. 1 58 67 M y 195

flocculation tests total serum protein serum alkaline phosphatase serum calcium and fecal fat determinations albumin globulin ratio prothrombin time histamine gastric analysis and gastric biopsy

Outstanding clinical features were weight loss (often severe) intermittent diarrhea glossitis latent tetany and anemia Frank steatorrhea was not invariably present in all stages of the disease The main biochemical features were hypoproteinemia hypocalcemia hypoprothrombinemia abnormal oral sugar tolerance curve low fasting level of total serum lipid and flat oral fat tolerance curve

The patients with idiopathic insufficiency had almost flat glucose tolerance curves whereas the patient with a gastrocolic fistula had a very low fasting blood sugar level However it showed a good rise and returned to fasting level in 1½ hours The patient with reticulosis had a fasting glucose level of 88 mg/cc which rose slowly to 160 mg in three hours after ingestion of 50 Gm glucose Improvement was noted after therapy

One of the outstanding features of this syndrome is the low level of total serum lipids (400 500 mg/cc) plus a low flat curve after administration of 50 Gm butter as estimated by the turbidimetric method of Kunkel for five to six hours Since the three patients given the oral glycine absorption test showed a marked increase in alpha amino nitrogen it appears that absorption of amino acid was not impaired

Diagnosis is not difficult when the more florid manifestations appear together but mild and atypical cases are commonly missed Intermittent diarrhea of unknown cause refractory iron deficiency or macrocytic anemia unexplained bleeding tendency (hypoprothrombinemia from impaired absorption of vitamin K) and the syndrome of osteomalacia should suggest malabsorption

Differentiation of symptomatic from idiopathic forms is important and not easy on clinical grounds alone Sugar tolerance curves may help and x ray study is of considerable importance In idiopathic steatorrhea gastric dilatation and megacolon indicate some intestinal atony and the small bowel deficiency pattern may appear These may also be present

in symptomatic cases Laparotomy is justified when doubt exists

Several mechanisms may cause the same pattern of mal absorption including deflection of stomach contents into the colon (inadvertent gastroterminal ileostomy or ileocolostomy as in regional ileitis) mechanically impaired fat adsorption (tuberculosis lymphadenoma or reticulosarcoma) and an inherited or acquired biochemical lesion (sprue)

In treatment a low fat high protein regimen should be supplied with general vitamin supplements The hematologic response to crude liver folic acid or vitamin B_{12} can be estimated only by trial and error

Disordered Gastrointestinal Function and Its Relationship to Tropical Sprue, Celiac Disease and Idiopathic Steatorrhea A C Frazer[8] (Univ of Birmingham) performed absorption secretion and motility studies in 10 patients with tropical sprue 10 with celiac disease and 24 with idiopathic steatorrhea All three conditions showed delayed and depressed intestinal absorption Pancreatic enzymes were within normal limits Radiographic studies showed excessive mucous secretion and decreased intestinal tone and motility in all three conditions The increased mucus caused flocculation of a simple suspension of barium sulfate and this reaction was found to be the true explanation of the so called deficiency pattern Use of simple suspensions of barium sulfate always showed pronounced flocculation in the upper small intestine (Fig 88) a phenomenon noted in normal subjects only rarely after a heavy fatty meal This did not occur if a nonflocculable preparation such as raybar was used (Fig 89) Functional incapacity of the small intestine is believed to be the basic pathologic lesion common to all three diseases Delayed and depressed absorption may cause calorie loss increased bacterial growth in the intestine and modification of intestinal contents These changes may be responsible for the main features of the syndromes observed

Of the various primary etiologic factors proposed there is no satisfactory experimental support for adrenal insufficiency vitamin deficiency or climate. Hereditary factors and infection may be causative in any of the three conditions

(8) T R y Soc T p M d & Hyg 46 576-598 N mbe 1952

Fig 88 (t p) —So-c ll d defi e y p tt n obser d p t t w th t p cal pr fte u g flocculable pen o f b m sulf t N t l mped m sses f op qu m d m

Fig 89 (bott m) —S m p ti t wh n no flocculabl s pe f ba m ll ta s us d N te w d ly d l t d hypot c appe ce of the m ll t t nd b se c f both l mp a d m l f the y p tt n (C u t f F a A C Tr R y Soc T op Med & Hyg 46 576 598 Nov mber 195)

Rancid fats may be important in tropical sprue whereas wheat gluten is undoubtedly a major factor in celiac disease

Studies on Etiology of Sprue Syndrome were conducted by A C Frazer[9] (Birmingham United Hosp) in 24 cases of idiopathic steatorrhea by the following methods (1) assessing fat absorption (2) examining intestinal pancreatic enzyme activity by intubation and investigating changes in fat after ingestion (3) measuring systemic hyperlipemia after dose of fat by chylomicrograph (4) assessing glucose and urea absorption from the upper small intestine by intraduodenal drip and (5) x ray examination of the upper small intestine with (*a*) flocculable and (*b*) nonflocculable barium sulfate suspension At least four of the five methods were used in all cases

Mean fat absorption was 73% (*range* 56-86%) with normal 95 plus or minus 4% Amylase lipase and trypsin levels were about normal in 18 and the fat was finely emulsified in the small intestinal lumen Six patients did not have intubation The chylomicrograph was flattened and delayed in 22 patients and not used in 2 All oral glucose tolerance curves were flat with variable rise after 40 minutes and delayed return to normal Urea absorption was similar to glucose All patients showed flocculation pattern with water suspended barium sulfate whereas those examined with nonflocculable suspension showed small intestinal atony

The fat absorption defect did *not* seem due to inadequate preparation of the fat since lipase and bile salts were found and ingested fat was finely emulsified in the intestinal lumen this is in striking contrast to patients with pancreatic enzyme deficiency Nonetheless particulate absorption as judged by systemic hyperlipemia seemed delayed and of less than normal amplitude Such defect might arise from some mechanical barrier (excessive mucus secretion) some intracellular fault (defective phosphorylation) or from inadequate intestinal motility

That glucose and urea absorption studies showed similar defects is strong evidence against a common phosphorylation fault Experimental evidence suggests that the x ray flocculation pattern is due to flocculation of barium by mucus Similar changes appear in normal subjects given fatty acids Excessive mucous secretion might interfere with particulate

(9) G t oe t I gu 78 357 364 1952

absorption of neutral fats and greater formation and absorption of fatty acids may result A vicious circle may then start excessive mucus more fatty acid increased mucous secretion Since no flocculation pattern is seen in the sprue syndrome when nonflocculable barium suspension is used the pattern is due to mucus

Cause and effect of the atony and decreased movement of the upper small intestine is not as yet clear

[Any serious attempt to determine the etiology of a disease entity or syndrome requires great skill and courage is usually beset with many difficulties and conclusions are usually challenged Frazer is a well known investigator in this field and his conclusions deserve respectful attention Apparently he has disproved the theory that the underlying biochemical defect involving several dietary constituents is a failure of phosphorylation That the radiologic flocculation pattern is due to an excess of mucous secretion that large dilated coils of small intestine are visualized and the basis of impaired motility are original significant observations Results of his further investigations in this difficult field will be eagerly awaited

The magnitude and variability of the absorptive defects in 11 patients with nontropical sprue has been the subject of an extensive metabolic study by Comfort Wollaeger Taylor and Power (Gastroenterology 23 155 178 1953) Fecal losses of fat reached 88% and those of nitrogen, 50% of the intake Fecal values for calcium phosphorus chloride, sodium and potassium tend to be greater than the average values reported for normal persons and may exceed the oral intake These abnormally larger fecal losses and resulting negative balance satisfactorily explain low blood or serum values for fat protein calcium phosphorus and potassium and also the occasional acidosis with hyponatremia and hypokalemia A diet high in caloric value protein carbohydrates and calcium and low in fat is necessary to compensate for the excessive loss of these substances in the feces —Ed]

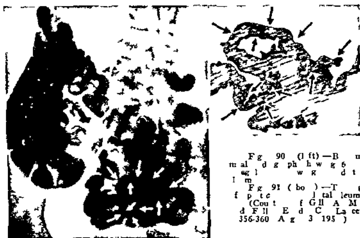
Recognition of Functional Disorders of Small Intestine A Morton Gill and Elizabeth de C Falle[1] discuss long standing obscure abdominal pain which was resistant to treatment in 8 (0 53%) of 1 500 new patients seen at the gastric clinic of West London Hospital in 1948 51

Woman 34 had had intermittent diarrhea aching lower abdominal pain radiating to the left sacroiliac joint and down the front of both thighs indifferent appetite and fulness and belching after meals for five years Apart from abdominal distention and an appendectomy scar nothing abnormal was found on physical examination or laboratory study A barium meal showed 6 in of irregular narrowing in the distal ileum (Figs 90 and 91) Laparotomy revealed nothing abnormal

All patients were nulliparous women whose first symptoms had appeared during the childbearing age Dysmenorrhea was usual All had abdominal pain poorly localized often radi

(1) La t 356-360 A g 3 1952

ating to the sacrum groins or anterior thighs aggravated by menstruation and defecation but unaffected by food holidays antispasmodics or hospital rest The women were energetic and overly conscientious with average to good intelligence Their personalities were immature but they had adapted well to their life situations All underwent laparotomy without organic findings Clinical examination revealed abdominal distention and tenderness with variable spasticity of the colon Intestinal x ray showed spasm mucosal thickening hyper motility or a deficiency pattern and the ileum was consistently



F g 90 (l ft) —B m m al d g ph h w g 6 eg l w g d t l I m
F g 91 (bo) —T g f p t e l tal leum (Cou t f G ll A M d F ll E d C La cet 356-360 A g 3 195)

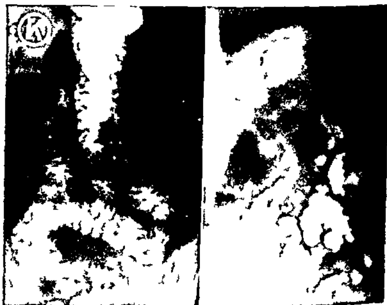
affected Inconstant features included pyrexia bladder dis turbances poor peripheral circulation and allergic symptoms

Colon spasm alone is 10 times more common is closely related to manifest anxiety has a well defined clinical picture and responds well to reassurance belladonna and phenobar bital The ileal syndrome however is less obviously psycho somatic in origin has a more complex symptomatology and is more resistant to treatment Although the two syndromes are usually distinct one patient in the group showed some features of both simultaneously

Disorders of Motility of Small Bowel. Ian W MacPhee[2] (Univ of Liverpool) describes a peculiar type of disorder

(2) La t 1 678 679 Ap 4 1953

found in 4 of over 400 cases of subtotal gastrectomy an incidence of about 1% Its specific radiologic appearance is segmentation of the small bowel contents When present the normal feathery appearance of the jejunum and ileum is lost and the barium collects into distinct aggregations separated by areas of spasm (Fig 92) Segmentation persists for an hour or more indicating continued segmental spasm of the gut Passage of the meal especially the dextrose barium



F g 92—Sm ll bow l aft btot l ga t ctomy l ft norm l ght segm tat (C rt sy f M Phee I W La t 1 678 679 Apr 4 1953)

meal is slowed in the small intestine even though the symptoms suggest small bowel hurry The condition is best illustrated in the following case

Man 31 underwent subtotal Polya type valved gastrectomy on Mar 10 1950 for chronic duodenal ulcer after which he had general debility abdominal pain after meals and diarrhea On October 12 hemoglobin value was 101% On October 24 the total amount of fat in the stools was 69% by weight of dried feces 596% being split and 404% not split Fat balance study showed 86% absorption. Hexamethonium bromide 250 mg three times daily after meals produced no improvement On Mar 6 1951 symptoms persisted and there was no improvement on various vitamin B factors On

Nov 12 1951 he was admitted with edema of ankles and legs abdominal pain after meals severe riboflavin deficiency and dyspnea Hemoglobin value was 82% reticulocytes 8% and plasma proteins 5 15 Gm./100 ml Feces showed undigested meat fibers and fat Despite massive parenteral vitamin B therapy riboflavin deficiency persisted the hypochromic anemia did not respond to iron orally or intravenously Symptoms were not relieved by treatment with folic acid hexamethonium bromide or belladonna during the next three months After a meal the patient had to rest for an hour during which time the abdominal pain persisted Glucose tolerance curves showed no evidence of hypoglycemia

All patients experienced considerable abdominal pain across the umbilicus starting immediately after meals and lasting up to an hour Some relief was obtained by reducing the carbohydrate content of the meal All four had diarrhea although the movement was not usually fluid and the bowels rarely moved more than three or four times daily The feces were light sometimes clay colored and contained a high proportion of split and unsplit fat with about 70 85% absorption As other evidence of deficient absorption there was severe hypochromic anemia in three cases and riboflavin deficiency in two These features both clinical and radiologic somewhat resemble idiopathic steatorrhea Subtotal gastrectomy seems to unmask an inherent bowel defect of deficient absorption associated with an abnormal motility pattern

[The author cited the investigations along similar lines of other British colleagues For example Glazebrook and Welbourn (Brit. J Surg 40 111 September 1952) concluded that increased motor activity in the jejunum provided adequate stimulus for the production of the efferent loop dumping syndrome and postgastrectomy steatorrhea —Ed]

Amebiasis Complement Fixation Test in Diagnosis of Intestinal Amebiasis A new antigen for the serologic diagnosis of amebiasis by a complement fixation test was prepared by M C McCowen of the Lilly Research Laboratories from a strain of E. histolytica grown on an egg slant medium in the presence of one associated bacterium F Steigmann W H Shlaes S Mintzer and G Schaefer[3] (Chicago) used this antigen with the serum of 90 patients having gastrointestinal disturbances and 10 controls Three stools collected on alternate days were examined for parasites When the first stool was submitted 10 cc blood drawn from the fasting patient was centrifuged and the serum sent to Lilly Research Laboratories

(3) G t be t logy 23 70 73 J 1953

where the complement fixation test was performed according to a modified Bengston technic

Positive results for both stool and complement fixation were obtained in 48 cases (48%) and negative results for both in 32 cases Negative stool and positive complement fixation results were found in 6 and positive stool and negative complement fixation in 14 Of the 10 controls 8 had negative stool and negative complement fixation results and 2 had negative stool and positive complement fixation results Thus in 80% the cases correlate Of special interest were those patients with ulcerative colitis who had negative stools and negative complement fixation tests with no false positives The authors recommend further clinical evaluation

Evaluation of Newer Amebacides was undertaken by Julio Sanchez Vegas[4] (Caracas Venezuela) in 264 cases of amebiasis followed for 6 24 months Neither aureomycin nor chloramphenicol proved satisfactory although they may be useful in eliminating trophozoites and subjective complaints Bismuth glycolylarsanilate (milibis®) and terramycin used singly produced satisfactory results in only 16% and 41% of patients respectively A combination of the two eliminated both cysts and trophozoites in 77 3% Thus the combination of a nonabsorbable and an absorbable amebacide proved the most effective attack suggesting that amebiasis should be considered a systemic disease rather than a purely intestinal or extraintestinal infection

Next 102 patients were given two types of experiment l bismuth glycolylarsanilate and chloroquine diphosphate (milibis® aralen®) tablets Group 1 consisting of 82 patients received 2 tablets each containing 500 mg bismuth glycolylarsanilate and 150 mg chloroquine daily for 15 days The 20 patients in group 2 were given 3 tablets containing 400 mg plus 100 mg daily for three days followed by a day of rest then 2 tablets daily for eight days Of group 1 82 9% showed favorable results as compared with only 20% in group 2 Moreover the group 1 dosage produced fewer and less marked side reactions Of all 102 patients treated with bismuth glycolylarsanilate and chloroquine 91 (89 2%) finally became free of cysts making this the most effective amebacide yet studied

[Current trend in the treatment of amebiasis undoubtedly is characterized by combination of an ar enical of which carbarsone is representa

(4) J A M A 151 1059 1065 Ma 8 1953

tive and one of the antimalarial quinoline compounds among which are chloroquine and diodoquin.® The therapeutic and prophylactic efficacy of milibis® and aralen® were also reported on by Berberian and associates in the 1952 YEAR BOOK (pp 676-677) —Ed]

Acute Porphyria Case Report with Use of Urecholine® in Management of Obstipation is presented by Charles Robinson John H Harbour and Kemp Plummer[5] (McGuire VA Hosp Richmond Va)

Man 25 was hospitalized after three days of localized constant aching epigastric pain with vomiting following alcoholic overindulgence He had had similar but milder episodes for three years He was acutely ill Mucous membranes and skin were dry Abdomen was flat with moderate epigastric tenderness but no spasm There were no other significant physical signs On admission laboratory results were *normal* except for 20% bromsulfalein retention in 45 minutes and a faint trace of albuminuria Upper gastrointestinal x ray series showed delayed gastric emptying

All disturbances except muscle weakness and fatigue responded to ulcer management and demerol® He was discharged after two weeks but relapsed three days later The myasthenia had progressed and the abdominal pain had returned followed by flaccid paralysis of the arms shoulder girdle and then both legs which last gradually improved When he was readmitted with a diagnosis of muscular dystrophy 10 weeks after onset he had lost 57 lb Pronounced generalized muscular atrophy and weakness were present Blood pressure varied from 100/60 to 150/110 Abdominal cramps became much more severe aggravated by persistent nausea retching and vomiting Cerebrospinal fluid was normal Small bowel x ray series showed delayed motility The Watson Schwartz test for urinary porphobilinogen gave *strongly* positive results and exposure of urine to sunlight caused it to turn a dark port wine color

Treatment was the same as before Obstipation a constant characteristic requiring enemas every day or two was relieved by 10 mg urecholine® subcutaneously three times daily and later the same dose orally but abdominal pain persisted Additional treatment with testosterone folic acid and vitamin B_1 produced no significant change Abdominal symptoms slowly abated and increasing muscular strength became evident under physiotherapy An emotional upset produced a *mild* relapse and return of pain During another relapse four months later he became acutely psychotic but there was spontaneous clearance within two weeks

Treatment for this condition thus far has been mainly symptomatic ACTH has been tried on at least one occasion without effect Since spontaneous remission is frequent nonspecific therapy often suffices for the acute attack Various stress factors—chemical drug or psychic—can provoke an acute

(5) Gastroenterology 20 662-666 Apr 1952

where the complement fixation test was performed according to a modified Bengston technic

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(4) J.A.M.A. 151 1059 1065 Mar 8 1953

Seventy five patients satisfied all of the following criteria acute constipation or diarrhea localized abdominal cramps *localized (usually left lower quadrant) muscle guard or* marked tenderness fever and leukocytosis Diverticulitis can be present without this complete picture especially fever and leukocytosis but patients lacking any of the criteria were *excluded because validity of the diagnosis could be questioned* Of the 75 56 had more than one attack

There was a tendency for diverticulitis to occur more often in patients with widespread diverticulosis of 15 with solitary *pockets none had inflammatory complication* In the 75 representing several hundred attacks gross hemorrhage occurred seven times perforation with localized peritonitis twice peridiverticular abscess once Acute obstruction occurred *frequently but lasted only three or four days Chronic obstruction* and fistula formation the two universal surgical indications were not seen Carcinoma developed in three diverticulosis patients but was found without difficulty Complications *indicating surgery occurred in 13 3% if gross hemorrhage is* included in 4% otherwise but in no case was surgery necessary

Standard treatment initiated early of bed rest liquid diet heat to the abdomen and administration of antispasmodics chemotherapy and mineral oil was followed All but four patients were treated at home Sulfasuxidine* and sulfathalidine* 2 3 Gm four times daily were agents most often used Aureomycin terramycin and chloramphenicol were not available during most of the period

If diverticulitis is treated early it rarely becomes a surgical problem

Potassium Balance in Ulcerative Colitis. Potassium deficiency reported occasionally in chronic ulcerative colitis may be a potential complication in prolonged severe exacerbations of the disease when there is anorexia with little or no intake of potassium and continued loss of potassium in the urine possibly in vomitus and especially in diarrhea H Marvin Pollard and Robert J Bolt[8] (Univ of Michigan) were unable to demonstrate conclusively the presence of significant hypokaliemia in 19 patients with active ulcerative colitis by simple

(8) G t oe ter l gy 2 564-574 Dec mbe 195

attack Because of neurologic aspects this condition should be kept in mind particularly by those who deal largely with neuropsychiatric disturbances

Painful Anal Lesions in Intestinal Disease are often the patient's chief complaint according to J Arnold Bargen and Raymond J Jackman[6] (Mayo Clinic) Symptomatic treatment which will in no way affect the progress of the main disease directly may have such a salutory effect on the patient's general condition that improvement is more rapid Suppositories containing ethyl aminobenzoate (benzocaine) help to control thrombosed hemorrhoids ulcers and abrasions With such lesions there is usually enough muscle spasm to push the suppository up into the rectum otherwise it is extruded immediately after insertion To avoid this and to keep the suppository in place the patient is advised to lie down and after lubricating the end of the suppository to insert it into the anal canal for ½ ¾ in holding the end with a piece of gauze When the suppository starts to melt it can be pushed on up into the rectum When the irritation is just inside or around the anal canal the medication may be applied as a dusting powder Other helpful symptomatic measures include use of dibucaine anal irrigations and witch hazel instilled into the rectum or applied locally with gauze packs

Surgery is contraindicated for thrombosed hemorrhoids or during exacerbations of ulcerative colitis During remission or relative quiescence of ulcerative colitis fistulas may be safely treated surgically Healing of anorectal conditions after operation for chronic colitis is usually prolonged but satisfactory

Study of Diverticulitis of Colon in Office Practice Believing that the reported incidence of surgical complications in diverticulitis of the colon (10-45%) is high probably because most reports come from hospital wards John L Horner[7] (St Louis) studied during 10 years 364 private office patients found by barium enema to have diverticula A disproportionately large percentage were in the advanced decades and 58 5% were women Diverticula were restricted to the sigmoid in 48% and were in combination with other segments in 43 5% The descending colon was involved in 48%

(6) Journal Lan t 2 530-53 November 1952
(7) G t oent ology 21 223 2 9 June 1952

Adequate dietary intake of potassium in uncomplicated but active ulcerative colitis is sufficient to prevent the development of hypokalemia Supplementary potassium administration when the patient is eating a good general diet is unnecessary With an inadequate diet with or without vomiting but with persistent diarrhea hypokalemia is a definite

BALANCE STUDIES IN ACUTE TOXIC PHASE OF ULCERATIVE COLITIS DURING CONTINUOUS SUCTION OF SMALL BOWEL

		INTAKE			OUTPUT				
		ORAL	I.V.	TOTAL	UR.	SUCTION	TOTAL	BAL	SERUM
[illegible]	Na	0	775	775	224	983	2 3	-43.8	30
	K	0	402	402	30.25	1.49	4 74	154	3.75
[illegible]	N	0	55	55	159	3 4	392	+15.8	
	K	0	0	0	23	2	250	250	
[illegible]	N	337	300	333.7	6.2	19.4	276	+306	
	K	8	4	2	5	22	3.7	11	
[illegible]	Na	65.5	145	205	39 3	5.0	44.3	+66.2	27
	K	17	4	2	74.0	15	75.5	-54.3	4.6

possibility and 40 80 mEq potassium (3-6 Gm potassium chloride or 4-8 Gm potassium bicarbonate) should be given daily using care to maintain an adequate renal output

Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine Lester M Morrison[9] (College of Med Evangelists Los Angeles) compares results obtained in 60 patients treated and studied for three years and 60 controls treated *with other current methods* The average dose of salicylazosulfapyridine was 1.5 Gm (three tablets) every three hours during the day for two weeks After a two week rest the drug was repeated for two weeks once or oftener as required Additional therapy included a bland diet oral supplements of multivitamins and when necessary antispasmodics sedatives or opium derivatives In 13 patients (21%) such toxic effects as headache nausea painful joints dermatitis and sometimes secondary anemia forced discontinuance of the drug after which symptoms promptly disappeared Of the 47 patients tolerant to treatment 11 (18%) remained symptom free after two to three courses during the entire observation period 31 (53%) were improved 14 (24%) remained rela

(9) J A M A 151 366-368 J 31 1953

measurement of serum potassium Of 79 determinations in the 19 patients 72 were within normal range (4 1 5 6 mEq/L) 4 slightly above and 3 below (Fig 93) None of the patients with elevated values had symptoms suggestive of hyper kaliemia

That intracellular potassium deficit may occur without noticeable changes in the serum potassium levels has been suggested by many observers To determine the presence or absence of an intracellular potassium deficit balance studies were done in two patients with active ulcerative colitis In the first patient potassium deficit was demonstrated by retention

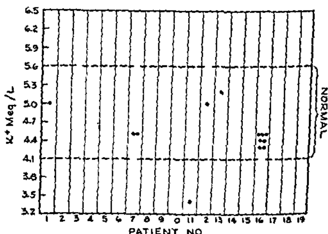


Fig 93—Serum potassium levels in 19 patients with chronic ulcerative colitis (Courtesy of Fell d H M and Bolt R J Gastroenterology 2 564 5 4 D m be 195)

when the patient was placed on a diet adequate in potassium A positive potassium balance was maintained despite a daily loss of about 40 mEq in the stool by a reduction in the urinary excretion That the deficiency was not marked was shown by the fact that the addition of 60 mEq potassium to the daily diet resulted in a marked increase in urinary potassium excretion on the third day throwing the patient into a negative potassium balance In the second patient negative potassium balance was seen during a period of small bowel drainage (table) This same situation would be expected to take place in the presence of vomiting or low food (potassium) intake and continued diarrhea

Adequate dietary intake of potassium in uncomplicated but active ulcerative colitis is sufficient to prevent the development of hypokaliemia Supplementary potassium administration when the patient is eating a good general diet is unnecessary With an inadequate diet with or without vomiting but with persistent diarrhea hypokaliemia is a definite

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		INTAKE			OUTPUT				
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[illegible]	N	0	75	775	22 8	98.5	12 3	-43.8	30
	K	0	40 2	40.2	50 25	11 1	4 7	15.4	3.75
[illegible]	N	0	55	55	59	6	72	+15.8	
	K	0	0	0	23	27	250	-250	
[illegible]	N	337	300	333 7	8.2	54	276	+306	
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	K	7	4	2	74.0	5	75 5	-54.3	4 6

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(9) J A M A 151 366 368 J 31 1953

tively unchanged and 4 (5%) grew worse after 2 10 courses within the same period

In the three years preceding the study 60 similar patients were treated under the same clinical conditions with diet liver extract parenterally and vitamin B complex therapy a course of sulfasuxadine* aureomycin or chloramphenicol combined with antispasmodics and sedatives or opium derivatives Four patients had formal psychotherapy After the initial course of treatment 3 (5%) remained symptom free throughout the follow up 19 (32%) were improved, 30 (50%) remained the same and 5 (8%) grew worse after intermittent courses during the same period Improvement in both series was measured by reduction of fever disappearance or substantial reduction of pain and the number of stools blood and mucus passed and increased weight appetite and a visible sense of well being within a few days of onset of therapy

The variability of patient response to the amount of drug was an outstanding feature of salicylazosulfapyridine therapy Some did well on as little as 2 tablets (1 Gm) three to four times a day whereas others required as much as 4-6 tablets every three hours Some patients intolerant to the drug were able to resume therapy if adjuvant medicinals such as dramamine* pyribenzamine* antacids or frequent milk feedings were ingested simultaneously Moreover Morrison recently noted that a combination such as 1 Gm (2 tablets) of the drug after meals and at bedtime with 25 mg cortisone three to four times a day often brought immediate and striking remission of the disease as compared to indifferent results with larger doses of either drug alone He concludes that salicylazosulfapyridine is useful in chronic ulcerative colitis and should be investigated further to increase its tolerance and effectiveness

On Incidence of Carcinoma in Chronic Ulcerative Colitis. Sadao Otani and Isidor Snapper[1] state that although many patients have both chronic ulcerative colitis and carcinoma of the colon the conclusion that carcinoma is secondary to the chronic inflammatory process is not justified These entities may become coexistent in many ways Multiple familial polyposis of the colon often leads to malignant change and often causes chronic ulcerative colitis Sometimes this basic pattern is not obvious because most nonmalignant adenomatous

(1) J Mt. Sinai H p 19 275 88 May June 1952



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polyps have been destroyed by the secondary ulcerative process or because there were not too many to begin with Adenomatous polyps can still be recognized as such since they contain dedifferentiated mucous glands which distinguish them from inflammatory polyps with low colonic mucosa

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(1) J Mt. Sinai Hosp 19 275 288 May June 1952

for the patient as a whole and planned diversional therapy

The effect of nervous stimuli on the colon can be partly inhibited by 1 mg atropine or 100 mg bathine* especially when taken at bedtime with a barbiturate As opiates induce colonic spasm they are usually contraindicated Predominant bacteria in the colon may be inhibited briefly by the various antibiotics but since drug resistant organisms soon grow out interrupted therapy is advisable Cold liquids residue and seasoning in the diet should be restricted but the value of dietary restriction must be balanced against the need for adequate nutrition If the patient becomes malnourished smaller meals with high caloric interval feedings hyperalimentation with whole protein liquid foods and specific vitamin and mineral supplements when necessary are indicated The use of ACTH and cortisone is often associated with striking weight gain apparently due to increased appetite However the ability of ACTH to inhibit cellular reactions to injury and to delay wound healing may be undesirable

Management of the patient s life stresses and emotional reactions is essential to recovery and the prevention of relapses Onset of the disease or its exacerbation usually coincides with a life situation which challenges the sensitive intelligent but immature person to play a mature and responsible role The physician can best think of him as a child and of himself as a parent The patient must first become confident that his doctor is devoted to his be t interests and will stop at nothing to help him All therapeutic measures should be introduced by one physician but the more unpleasant ones should be done by someone else with the personal physician in the role of sympathetic friend Frequent visits and many acts of kindness beyond medical treatment further strengthen the patient s confidence and he comes to identify himself with his doctor When improvement is well advanced the physician parent loosens the ties by encouraging a wider range of social contacts and giving his strong approval of them This pattern of psychotherapy has proved most effective in ulcerative colitis The unearthing and verbal review of deeply buried emotional conflicts is usually undesirable

There is no effective medical therapy for regional enteritis partly because so little is known of its etiology Bed rest is advisable during febrile periods and modified rest otherwise

(Figs 94 and 95) Thus adenomatous polyps may often be found in a colon in which chronic ulceration and carcinoma are also found

Multiple areas of carcinoma in the colon are caused by multicentric malignant degeneration of adenomatous polyps and cannot be metastases from a solitary carcinoma of the colon secondary to ulcerative colitis It should also be emphasized that localized ulcerative colitis often arises near and secondary to a stenosing carcinoma The fact that adenomatous polyps are found in long standing ulcerative colitis is important because they may actually be responsible for the carcinoma formation

A patient in whom carcinoma first developed from malignant degeneration of an adenomatous polyp is discussed Five years later ulcerative colitis appeared If it had appeared before the malignant degeneration carcinoma might wrongly have been attributed to nonspecific colitis

[The authors observations give much food for thought Johnson and Orr (1948) also described the development of carcinoma from adenomatous polyps in patients with chronic ulcerative colitis The incidence of carcinoma is significantly greater in patients with this disease than in the general population especially in those in whom the disease is of long duration and in patients undergoing operation In the latter group the presence of carcinoma was frequently unsuspected Perhaps too strong a case has been made for familial polyposis as a precursor The role of incidental or poradic polyps is more convincing The significance of adenomatous polyp to adenocarcinoma of the colon is indisputable.

On the other hand some authorities maintain that pseudopolyps (inflammatory polyps) play the major role in carcinomatous transformation This is contrary to the opinion of Otani and Snapper who subscribe to Ewing s conviction that the transformation of an inflammatory process to neoplasm is very rare It does not seem reasonable to dismiss the possibility that a disorganized degenerated mucosa resulting from chronic recurring inflammation and infection is a suitable soil for the development of carcinoma Counsell and Dukes observed that carcinoma frequently develops without any vi ible or recognizable neoplastic lesion on the surface It may be an oversimplif cation to conclude that most if not all carcinomas in as ociation with chronic ulcerative colitis had their origin in adenomatous polyps —Ed]

Medical Management of Ulcerative Colitis and Regional Enteritis should according to Thomas P Almy (Cornell Univ) be based on the following bedside observations (1) the patient has a hyperactive colon which is the site of a serious inflammation (2) he is usually nutritionally depleted is fearful depressed and discouraged and has variable infantile traits Although general improvement usually follows ileostomy similar results can be attained medically with rest

(2) B ll N w York Acad Med 28 693-699 N vembe 1

for the patient as a whole and planned diversional therapy

The effect of nervous stimuli on the colon can be partly inhibited by 1 mg atropine or 100 mg bathine* especially when taken at bedtime with a barbiturate As opiates induce colonic spasm they are usually contraindicated Predominant bacteria in the colon may be inhibited briefly by the various antibiotics but since drug resistant organisms soon grow out interrupted therapy is advisable Cold liquids residue and seasoning in the diet should be restricted but the value of dietary restriction must be balanced against the need for adequate nutrition If the patient becomes malnourished smaller meals with high caloric interval feedings hyperalimentation with whole protein liquid foods and specific vitamin and mineral supplements when necessary are indicated The use of ACTH and cortisone is often associated with striking weight gain apparently due to increased appetite However the ability of ACTH to inhibit cellular reactions to injury and to delay wound healing may be undesirable

Management of the patient s life stresses and emotional reactions is essential to recovery and the prevention of relapses Onset of the disease or its exacerbation usually coincides with a life situation which challenges the sensitive intelligent but immature person to play a mature and responsible role The physician can best think of him as a child and of himself as a parent The patient must first become confident that his doctor is devoted to his best interests and will stop at nothing to help him All therapeutic measures should be introduced by one physician but the more unpleasant ones should be done by someone else with the personal physician in the role of sympathetic friend Frequent visits and many acts of kindness beyond medical treatment further strengthen the patient s confidence and he comes to identify himself with his doctor When improvement is well advanced the physician parent loosens the ties by encouraging a wider range of social contacts and giving his strong approval of them This pattern of psychotherapy has proved most effective in ulcerative colitis The unearthing and verbal review of deeply buried emotional conflicts is usually undesirable

There is no effective medical therapy for regional enteritis partly because so little is known of its etiology Bed rest is advisable during febrile periods and modified rest otherwise

(Figs 94 and 95) Thus adenomatous polyps may often be found in a colon in which chronic ulceration and carcinoma are also found

Multiple areas of carcinoma in the colon are caused by multicentric malignant degeneration of adenomatous polyps and cannot be metastases from a solitary carcinoma of the colon secondary to ulcerative colitis It should also be emphasized that localized ulcerative colitis often arises near and secondary to a stenosing carcinoma The fact that adenomatous polyps are found in long standing ulcerative colitis is important because they may actually be responsible for the carcinoma formation

A patient in whom carcinoma first developed from malignant degeneration of an adenomatous polyp is discussed Five years later ulcerative colitis appeared If it had appeared before the malignant degeneration carcinoma might wrongly have been attributed to nonspecific colitis

[The authors observations give much food for thought. Johnson and Orr (1946) also described the development of carcinoma from adenomatous polyps in patients with chronic ulcerative colitis The incidence of carcinoma is significantly greater in patients with this disease than in the general population especially in those in whom the disease is of long duration and in patients undergoing operation In the latter group the presence of carcinoma was frequently unsuspected Perhaps too strong a case has been made for familial polyposis as a precursor The role of incidental or sporadic polyps is more convincing The significance of adenomatous polyp to adenocarcinoma of the colon is indisputable

On the other hand some authorities maintain that pseudopolyps (inflammatory polyps) play the major role in carcinomatous transformation This is contrary to the opinion of Otani and Snapper who subscribe to Ewing's conviction that the transformation of an inflammatory process to neoplasm is very rare It does not seem reasonable to dismiss the possibility that a disorganized degenerated mucosa resulting from chronic recurring inflammation and infection is a suitable soil for the development of carcinoma Counsell and Dukes observed that carcinoma frequently develops without any visible or recognizable neoplastic lesion on the surface It may be an oversimplification to conclude that most if not all carcinomas in association with chronic ulcerative colitis had their origin in adenomatous polyps —Ed]

Medical Management of Ulcerative Colitis and Regional Enteritis should according to Thomas P Almy (Cornell Univ) be based on the following bedside observations (1) the patient has a hyperactive colon which is the site of a serious inflammation (2) he is usually nutritionally depleted is fearful depressed and discouraged and has variable infantile traits Although general improvement usually follows ileostomy similar results can be attained medically with rest

(2) B ll N w Yo k A d M d 8 693 699 N mb r 195.

ment has been observed in 60 80% of patients given sulfon amides and in most patients on aureomycin and chloram phenicol Less favorable results have been reported with penicillin and streptomycin Since reduction in bacterial counts after these various agents is temporary rotating the drugs may be helpful If there has been any suspicion of amebic infection the authors administer a course of diodoquin *

Administration of ACTH is commonly followed by im provement in emotional state appetite nutrition diarrhea constitutional symptoms and proctoscopic picture However relapse often follows withdrawal of the drug At present ACTH seems to be useful in inducing remission in some patients This material and cortisone appear to act by dimin ishing inflammatory response in the disease

Since these patients may strongly resent psychiatric con sultation they may accept similar treatment if started by the psychiatrically oriented internist In few diseases is the per sonal relationship between patient and physician as important as *in ulcerative colitis Because exacerbations are often pro* tracted however the internist should be prepared to continue assuming responsibility for management for many months

[The preceding articles are representative of numerous ones on ulcera tive colitis Since its cause is unknown treatment is chiefly supportive and symptomatic apart from the psychiatr c and surgical a pects As in any disease adequate su tained treatment in the earlier tages has greatest prospects of success About ,c of cases can be classified as cured 50c satisfactorily controlled and 10c fatal Appraisal of the intrinsic thera peutic efficacy of any particular pharmacologic agent is difficult. For ex ample, the alterative effect often dramatic of corticotrophin is generally conceded Improvement on procto cop c examination has frequently been observed The favorable claims of long term results in patients so treated will be challenged Most autho ities regard th s form of therapy as es sent ally a temporary support ve measure Becau e the jo nts liver kid neys and skin are involved n chron c ulcerative colitis pathologists re ga d it as a relap ing acute and ch onic disease of the whole body most manifest pathologically in the colon —Ed]

A high protein low residue diet is used to repair obvious nutritional losses With psychotherapy many patients improve and some go into lasting remission When conservative measures fail ACTH and cortisone may produce short term remissions in some patients with greater involvement of the small bowel or severe diarrhea and vomiting Remissions may possibly be sustained by continued use of cortisone by mouth

Medical Management of Chronic Ulcerative Colitis, a disease of unknown etiology with a characteristic pathologic picture pronounced tendency toward chronicity and no specific therapy is discussed by Charles A Flood and Michael J Lepore[3] (New York City) Though long term cure is unlikely most patients seldom are completely incapacitated Efforts to implicate a specific causative organism or substance such as lysozyme have failed Increased attention has been given to psychologic factors such as emotional immaturity fright and resentment toward the disease

In the acutely ill patient maintenance of nutrition is of first importance Diarrhea causes loss of water blood and many other essential substances Correction of these disturbances depends on use of transfusions and other appropriate fluids for intravenous administration selected from mixtures of sodium and potassium chloride with or without glucose plus calcium and vitamins A K and B complex orally or parenterally These measures are supplementary to a high calorie moderately low residue diet

Since colon hypermotility appears to result mainly from the inflammatory process medications for reducing motility except for opiates are limited in their effectiveness Large doses of barbiturates may be used but atropine and belladonna have little effect on diarrhea Banthine® has limited value perhaps because the underlying mechanism involves the colon directly In some patients it has been useful in reducing diarrhea and depressing the gastrocolic reflex The authors use it but discontinue medication if beneficial effects do not appear within 48 hours Opium and its derivatives acting directly on smooth muscle are usually quite effective though possible addiction makes them less valuable

Use of anti effective drugs is justified for the protection of the acutely ill patient against secondary infection Improve

(3) New York J Med. 52 2265 2269 Sept. 15 1952

METABOLISM



ROBERT H. WILLIAMS M.D

PART VI

METABOLISM

THYROID GLAND

The most interesting recent developments regarding the thyroid are the studies with triiodothyronine Although found in the body in considerably smaller quantities than thyroxin it exerts a much more immediate calorigenic effect and thyrotrophin inhibitory effect It, like thyroxin is quite active by mouth

Preliminary studies with potassium perchlorate in the treatment of thyrotoxicosis have yielded promising results Possibly it will not be associated with agranulocytosis

The first report of follow up studies of a large series of patients prepared with antithyroid compounds for thyroidectomy shows no significant difference compared with iodide therapy in the incidence of myxedema and persistence or recurrence of thyrotoxicosis The results however are better with respect to survival thyroid storms hospital stay etc

Radioiodine is rapidly increasing in importance in the diagnosis and treatment of thyrotoxicosis In some clinics it is used more than surgery —Ed.

The Metabolic Activity of 3,5 3 1 Triiodothyronine in Myxedema is discussed by Samuel P Asper Jr Herbert A Selenkow and Charles A Plamondon[1] (Baltimore)

Since l thyroxin alleviates myxedema and occurs in plasma it is generally accepted as the thyroid hormone However several paradoxes exist (1) desiccated thyroid has greater calorigenic activity than accounted for by its l thyroxin content (2) unlike most hormones delay in specific effects is observed after exhibition and (3) in some athyrotic patients receiving l thyroxin the serum protein bound iodine level is higher than anticipated by their clinical and metabolic status Preliminary studies with the newly discovered l triiodothyronine in three myxedematous patients indicate that this compound produces an immediate metabolic effect 5 10 times that of equivalent amounts of l thyroxin (Fig 96) The remarkable activity of l triiodothyronine may afford explanation of these paradoxes

Within six hours of administration of 0 5 1 0 mg of l triiodothyronine in a single subcutaneous dose pulse rate and body temperature progressively increased reaching a maxi

(1) P oc Am. Soc. Cl n. I e t. p 7 M y 4 1953

showed acute deterioration in form but subsequent improvement

L-triiodothyronine alleviates myxedema more rapidly and with smaller doses than l thyroxin and may represent the functional constituent of the thyroid hormone

[This study along with those reported by several other investigators suggests that triiodothyronine plays an important role in thyroid physiology and that it exerts a more prompt calorigenic effect than thyroxin Whether triiodothyronine or thyroxin is the active form of the thyroid hormone has not been determined but the consensus seems to favor the former Just how commonly these compounds will be used in patients is difficult to estimate As long as they remain considerably more expensive than desiccated thyroid the latter will probably be used in most patients —Ed]

Effects of l Thyroxin Sodium on Nontoxic Goiter, Myxedema and Thyroid Uptake of Radioactive Iodine Solomon Papper Belton A Burrows Sidney H Ingbar John H Sisson and Joseph F Ross (Boston) state that synthetic thyroxin is apparently absorbed and physiologically active when ingested In all of seven patients with nontoxic goiters before and after two to eight weeks of orally administered l thyroxin sodium in daily doses of 0 1-0 2 mg uptake of I^{131} was suppressed The influence of l thyroxin administration on the size of nontoxic goiters was studied in 13 patients treated 3 12 weeks with an initial dose of 0 1 mg increased by 0 1 mg every four weeks if there was no response In one of the five with nodular goiter the mass disappeared In two of the eight with diffuse nontoxic goiter the thyroid returned to normal size and in four others the goiter definitely diminished Seven patients with previously untreated myxedema were given l thyroxin sodium in daily doses of 0 05 0 1 mg increments of 0 1 mg being added when the therapeutic response to the preceding dose had stabilized until a euthyroid state was attained Three patients who had been euthyroid while taking thyroid extract were changed to l thyroxin sodium in an initial ratio of 0 1 mg l thyroxin to 0 06 Gm (1 gr) thyroid extract Six of the previously untreated patients became euthyroid in three to eight weeks and were maintained on 0 2-0 3 mg daily One patient did not become euthyroid for 12 weeks and needed 0 5 mg daily The previously treated patients were maintained on 0 2 0 5 mg l thyroxin

The study shows that synthetic l thyroxin can suppress I^{131} uptake in euthyroid patients reduce the size of nontoxic

(2) New England J Med 247 897 899 Dec. 4 1952

mum on the third day Weight loss and diuresis also occurred The BMR increased promptly L triiodothyronine accelerated urinary creatine excretion moreover nitrogen and phosphorus diuresis developed resulting in negative nitrogen and phosphorus balances

After administration of equivalent amounts of l thyroxin significant but minimal metabolic changes occurred

Serum protein bound iodine levels increased after adminis

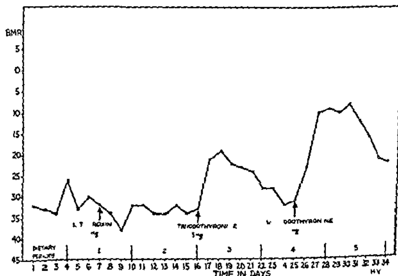


Fig 96.—Spontaneous idiopathic myxedema in woman aged 42 Basal metabolic rate was determined daily No significant alteration occurred after administration of 0 6 mg l thyroxin [illegible] However after administration of equimolar dose of 0 5 mg l triiodothyronine BMR increased rapidly from −33% to −19% After administration of 1 mg l triiodothyronine BMR changed from −32% to −9% (Courtesy of S P Asper Jr et al)

tration of l triiodothyronine but often remained in ranges found in hypothyroidism when the patients were metabolically euthyroid yet l thyroxin increased the value to levels found in euthyroidism although the patients remained hypothyroid Serum cholesterol levels decreased after administration of either l thyroxin or l triiodothyronine this decrement did not bear quantitative relationship to the degree of metabolic change observed Electrocardiograms revealed more rapid reversion to normal after l triiodothyronine than after l thyroxin After l triiodothyronine ballistocardiograms first

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( ) N w E gl d J M d 247 897 899 Dec 4 1952

goiters in some persons and induce remissions in patients with myxedema There is no difference between the action of l thyroxin and thyroid extract L thyroxin has the advantages of constant uniform strength and composition and greater stability

[Contrary to the opinion held for many years thyroxin has a powerful effect when given orally Just how much it will replace desiccated thyroid remains to be determined It does have the advantage of being a pure chemical compound and should exert a uniform effect —Ed.]

Effect of Exogenous Thyroxin on Radioiodine Uptake in Normal Subjects and in Cases of Thyrotoxicosis in Remission. Margaret E Morgans A K Oldham and W R Trotter[3] (Univ College Hosp London) studied radioiodine uptake before and at the end of a course of sodium l thyroxin (0 4 mg/day for two weeks given orally) in 20 normal subjects 13 patients with nontoxic goiters and 13 patients cured of thyrotoxicosis The dose of I^{131} for each subject before and after taking thyroxin was 10 μc The uptake was measured by the neck thigh ratio i e the ratio of the final neck Geiger count minus the preliminary neck count to the final thigh Geiger count minus the preliminary thigh count Geiger counters were placed at the same distance from the neck and from the thigh and readings taken simultaneously

A significant and very similar fall occurred in the neck thigh ratio in all three groups during thyroxin administration This evidence suggests that the abnormal increased uptake in thyrotoxic patients is confined to the active phases of thyrotoxicosis

An additional group on 10 normal subjects were given an equivalent dose of potassium iodide (0 3 mg/day for 14 days) to determine the effect of iodide per se They failed to show a significant decrease in neck thigh ratio thus indicating that the depression of the ratio in other subjects was not due to iodide released by the breakdown of thyroxin

[These observations are important in analyzing the pathogenesis of thyrotoxicosis Whereas thyroxin is shown to have similar inhibitory effects on thyroids of patients cured of thyrotoxicosis and of normal subjects there is less inhibitory effect when the thyrotoxicosis is present (J Clin Endocrinol 12 1561 1952) Even in patients cured of thyrotoxicosis there is a demonstrable hypernormal rate of uptake of I^{131} (Am J M Sc 223 495 1952) —Ed]

(3) J Endocrin l 8 250-253 July 1952

Mechanism Responsible for Altered Blood Cholesterol Content in Deranged Thyroid States Ray H Rosenman San ford O Byers and Meyer Friedman[4] (Mount Zion Hosp San Francisco) incorporated either powdered thyroid substance or thiouracil into the diets of rats to produce a hyper or a hypothyroid state These rats with normal controls were studied for (1) relationship of thyroid activity to plasma cholesterol (2) effect of dietary cholesterol on plasma choles terol (3) distribution of cholesterol (4) rate of cholesterol synthesis (5) rate of cholesterol elimination and destruction (6) relationship of bile acid metabolism to cholesterol me tabolism and (7) mechanism of effects of thyroid dysfunction on cholesterol metabolism

Results indicated that the hyperthyroid state is associated with a greatly increased rate of hepatic synthesis destruction and intestinal excretion of cholesterol The decreased concen tration of plasma cholesterol which occurs in the hyperthy roid state probably is due to the differences in degree of altera tions of synthesis and elimination of cholesterol On the other hand the greatly decreased rate of hepatic synthesis of cholesterol found in the hypothyroid state probably is associ ated with hypercholesteremia because of the more pronounced decrease in rates of destruction and intestinal excretion of cholesterol also present in this derangement

The disparity between altered synthesis and elimination seem to be related to a preceding disturbance in cholate me tabolism and to the effect of thyroxin on various intracellular enzyme activities concerned with anabolic and catabolic proc esses

[This helps explain the cholesteremic changes in different levels of thyroid function Whereas the blood cholesterol is very helpful in diag nosing myxedema it is not very helpful in diagnosing thyrotoxicosis —Ed]

Hypercholesteremia Myxedema and Atherosclerosis Herr man L Blumgart A Stone Freedberg and George S Kur land (Harvard Univ) report clinical and postmortem find ings in eight patients with rheumatic heart disease or cor pulmonale who had hypothyroidism or myxedema with ele vated cholesterol values and who survived 1 13 years fol lowing surgical total thyroidectomy There was an average

(4) J Cl E d 1 1 1 87 1 99 O t ber 195
(5) T A. Am. Phy n 65 114-1 0 1952

increase in blood cholesterol level of 125 mg./100 cc. above the pretreatment levels. None of the eight had complete occlusion of any of the coronary arteries. Five had no narrowing of any of the main stems or branches of the coronary arteries and only three had slight narrowing of one of the main stems. In the other arteries, atheromatosis and atherosclerosis varied greatly but were similar to conditions generally observed in similar euthyroid patients. The results do not disprove a role of cholesterol in production of atherosclerosis but demonstrate that over the observed period the hypothyroid state with its hypercholesteremia is not necessarily and by itself a sufficient cause of the production of coronary atherosclerosis.

Effect of Massive Cortisone Therapy on Measurements of Thyroid Function. Donald S. Fredrickson, Peter H. Forsham and George W. Thorn[6] (Harvard Med. School) measured the uptake of radioactive iodine by the thyroid in seven patients with normal thyroid function before and after administration of cortisone acetate, either orally or by intramuscular injection. Dosage ranged from 400 to 500 mg./day for several days to three weeks. All patients showed a great decrease in accumulation of I^{131} after cortisone administration. This was reflected in the proportional decreases in both the 24 hour percentage accumulation and the accumulation gradient. There was an average difference of 17.2 (expressed in absolute numbers) between the 24 hour control uptake and the 24 hour uptake during therapy. The average depression of I^{131} collection in 24 hours was about 50%. After cortisone therapy there was a significant increase in excretion of I^{131} in the urine.

Depression of the I^{131} accumulation in the thyroid after administration of cortisone may occur rapidly and persist for variable periods, depending on the route of administration of the steroid but apparently not on duration of treatment. The time required for thyroid recovery after cessation of therapy may be short (one or two days) if cortisone is given orally but prolonged (two to seven weeks) if the intramuscular route is used. This finding is consistent with the prolonged "depot" effect of cortisone given intramuscularly as compared with the effect of oral administration.

When thyrotrophin was given to one patient who had had

(6) Cl n E doc 1 1 541 553 M y 1952

a decrease in I^{131} uptake after cortisone administration a pronounced increase in uptake occurred

All patients showed a fall in protein bound iodine after cortisone therapy in some this was accompanied by a rise in serum cholesterol

The thyroid uptake of I^{131} was unchanged in two patients with classic exophthalmic goiter after administration of cortisone

The mechanism responsible for the decreased thyroid uptake of I^{131} is not completely understood Abnormal fixation of iodine to extrathyroid tissue may be responsible or there may be an increased excretion of iodine due to a primary renal effect of the steroid Further work will be necessary to ascertain whether within the thyroid cell itself there is a selective effect on the trapping of inorganic iodide or its incorporation into the organic molecule The effect of the pituitary on the thyroid under cortisone therapy must also be studied

[At least some of the decrease in uptake of iodine by the thyroid produced by ACTH and cortisone can be attributed to an increased excretion of iodine in the urine (Kuhl and Ziff J Clin Endocrinol 12 554-559 May 1952) —Ed]

Determination of Antithyroid Action of Para Aminosalicylic Acid Using Radioactive Iodine Åke Hanngren[7] (Uttran Sweden) studied the accumulation of iodine in the thyroid gland during para aminosalicylic acid (PAS) therapy

Iodine uptake after an oral dose of 0 1 mc of I^{131} reached a maximum of 35% of the given dose in 24 hours in one patient who had had no chemotherapy After three weeks of PAS therapy the patient was again given 0 1 mc of I^{131} and 2½ hours later when iodine uptake had reached 16% a total of 300 cc sodium PAS (10 5 Gm) was given intravenously over 1½ hours After about 45 minutes (when approximately half the PAS had been given) uptake of iodine in the thyroid stopped and no more iodine was taken up for 4 hours After 15 hours the thyroid had regained some of its ability to take up iodine The inhibitory action of the PAS probably ceased before the nonprotein bound iodine was excreted Findings similar to these were noted in two other patients

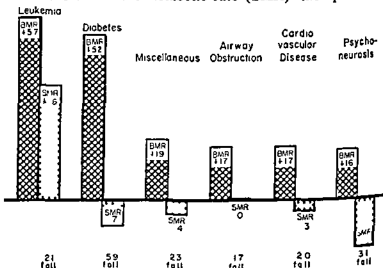
When PAS is given therapeutically a certain concentration in the blood inhibits the synthesis of thyroxin in the same way as thiouracil does Doses of PAS in excess of the pa

(7) La cet 2 117 J ly 19 1952

tient s thyroid sensitivity may give rise to myxedema and therefore before PAS is given the possibility of individual sensitivity should be considered

[With the common usage of PAS cognizance of its antithyroid effect should be taken The compound like thiouracil blocks the synthesis of thyroxin thereby producing myxedema and goiter —Ed]

Laboratory Diagnosis of Extrathyroidal Hypermetabolism Charles V Meckstroth Richard L Rapport George M. Curtis and Sarah Jane Simcox[8] (Ohio State Univ) tested the BMR the somnolent metabolic rate (SMR) the uptake and



F g 97 —E t thy d l hyp met b l sm ba l d som l t met b l tes. (C t y f M ck t th C V t al J Cl n E d nol 1 1373 13 9 Oct b r 195)

excretion of radioiodine and concentrations of serum protein bound iodine and of cholesterol in 49 patients with hypermetabolism Each had an elevated BMR and many had an initial diagnosis of hyperthyroidism In all of the patients the hypermetabolism was caused by extrathyroidal disease rather than hyperthyroidism Cerebral stimulation increased metabolism of malignant cells pregnancy pheochromocytoma alterations in hemodynamics such as occur in congestive heart failure and many other nonthyroid states can affect the metabolic rate The final diagnosis was leukemia in 6 patients diabetes in 3 airway obstruction in 5 cardiovascular disease in

(8) J Cl E do 1 12 1373 1379 O t be 1952

5 psychoneurosis in 11 and miscellaneous conditions in 18

The BMR alone is unreliable as an index of the cause of the hypermetabolism The relative effectiveness of further laboratory tests to aid in diagnosing extrathyroidal hypermetabolism is estimated at 95% for the protein bound iodine test 89% for the radioactive iodine test 72% for the cholesterol level and 53% for the SMR

The various tests employed are not comparable to each other since each measures a different aspect of the complex metabolism of the thyroid gland Radioactive iodine uptake measured by a single 24 hour count tells only how much *radioactive iodine is in the thyroid gland at that time* The serum protein bound iodine test measures the amount of circulating iodine bound to the protein molecule The SMR is a metabolic rate recorded under an ideal basal state It is especially valuable in such functional disorders as anxiety neuroses as it is void of all nervous and muscular factors Except for three diabetic patients the average fall of the SMR was greatest (31%) in psychoneurosis (Fig 97) The concentration of serum cholesterol is only an indirect test of *thyroid function*

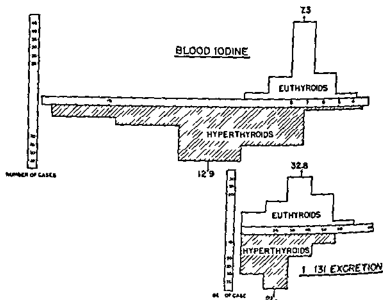
The study shows that many laboratory tests are required to reach the final diagnosis of extrathyroidal hypermetabolism

[The authors duly emphasize that there are several worthwhile tests for hyperthyroidism but that they may not be in accord since they measure different segments of metabolism The SMR test enjoys its greatest merit in eliminating the hypermetabolism that commonly accompanies anxiety neurosis —Ed]

Laboratory Aids in Diagnosis of Hyperthyroidism Solomon Silver and Sergei Feitelberg[9] (New York City) have worked out a new test based on the measure of radioactivity in the blood after tracer doses of I^{131} to refine further the diagnostic use of radioactive iodine The test depends on the fact that the hyperfunctioning gland should deliver larger amounts of hormone to the circulation than the normal gland Hormone formed after ingestion of I^{131} is labeled with the isotope and can be detected and measured in the circulating blood The labeled hormone circulates in a form bound to protein so that the measurement of protein bound I^{131} in the plasma should give some idea of the rate of delivery of newly formed hormone to the circulation This proved to be true

(9) J Mt S JI p 19 345 351 May June, 1952

in 310 observations on an equal number of euthyroid and hyperthyroid patients Not one euthyroid patient showed val ues within the hyperthyroid range A single specimen of a few cubic centimeters of blood drawn 72 hours after an oral tracer dose of 100 μc I^{131} will supply all necessary diagnostic information If the count in the whole plasma is low, no fur ther manipulation is required and hyperthyroidism can be



F g 98 —D t but n of thy d sm (85) nd hyp rthy d m (79) pl tt d c cord ng t blood od l l (I BI) d x t f I[131] E h ho zo tal di ep e ts o e tanda d d ti n n th pond g scale (Co t y of S l er S nd F t lbe g S J Mt S Hosp 19 345 351 May J e 195)

excluded with a high degree of certainty If the count in the whole plasma is high the plasma proteins have to be precip itated and washed and the activity due to protein bound I^{131} evaluated because only the protein bound I^{131} represents thyroid activity The inorganic I^{131} which may contribute to the radioactivity of the total plasma circulates only because it has not been excreted by the kidneys or trapped by the thyroid

This te t has been most helpful in all studies involving the use of I^{131} to diagnose thyroid activity Its value is destroyed if iodine in any form antithyroid drugs or thy oid extract

have been taken within a short time before the study is made

Figure 98 represents protein bound iodine and I^{131} excretion values obtained in a series of 85 euthyroid and 79 hyperthyroid patients in whom final diagnosis was certain The protein bound iodine showed a better correlation with the final diag nosis than the I^{131} excretion Figure 99 illustrates the data regarding 310 patients in whom the protein bound I^{131} of the

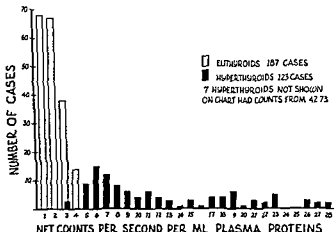


Fig 99 —Val es t cou t /se d of w shed p ote ns der ed f m 1 ml m t 72 h ft 100 μc ca f e I^{131} g e ally Four unts/ econd is 0 0003 μc I^{131} or 0 3% of th dm n t ed do /l t f pl ma (Cou tesy Sil S d F t lb g S J Mt. S na Ho p 19 345-351 May Jun 1952)

plasma was measured Whenever the activity exceeded 4 counts/second/ml plasma the patient was hyperthyroid In all but three instances euthyroid patients had counts below this level

[Some investigators prefer the concentration ratio (p otein bound to nonprotein bound radioiodine in the serum 24 hours after a tracer dose of iodine) to measurement of radioiodine in the urine or over the thyroid The principle related here is similar except that after 72 hours the thy roid has had a longer time to manufacture its hormone and the blood is freer of inorganic iodine thereby simplifying the test. This test is not subject to the pitfalls involved in urine collections and epithyroid counts It can be applied even in remote areas of the country because the tracer dose of radioiodine can be sent and the serum returned by mail to a com merc al laboratory for measurement of the radioiodine content —Ed.]

Effect of Perchlorate on Human Thyroid Gland John B Stanbury and James B Wyngaarden[1] (Massachusetts Gen l Hosp) *report observations on 12 patients with typical Graves*

(1) Metabol sm 1 533-539 Novembe 1952.

disease Three types of experiments were designed to determine whether perchlorate could displace iodide from the thyroid gland In one the subjects received a blocking dose of 1 methyl 2 mercaptoimidazole then a tracer dose of I^{131} and when I^{131} had accumulated in the gland $KClO_4$ orally In the second series $KClO_4$ was given before the tracer In the third the blocking drug was omitted and $KClO_4$ given before the tracer Measurements of isotope uptake in the gland were made with a lead shielded scintillation counter using a sodium iodide crystal

Aqueous potassium perchlorate when given orally in doses of 3 100 mg resulted in a rapid release of previously accumulated iodide from the thyroid glands of the subjects treated with 1 methyl 2 mercaptoimidazole Perchlorate also effectively inhibited the accumulation of I^{131} This action is qualitatively similar to that of thiocyanate Duration of inhibition of I^{131} uptake after a single dose of 100 mg perchlorate was about six hours No toxic effects of perchlorate were encountered in these patients who were given as much as 600 mg of the drug

Perchlorate is known to cause goiter in rats The experiments reported here suggest that perchlorate may be a suitable antithyroid agent for human therapeutics

[Whether this compound will prove to have a definite place in the treatment of thyrotoxicosis will depend upon the results of further study —Ed]

Metabolic, Isotopic and Pathologic Differences between Sodium 5 Iodo-2-Thiouracil and Thiouracil plus Potassium Iodide Boris Catz and Paul Starr[2] (Univ of Southern California) found that the maximal clinical response (average 13 76 days) and lack of goitrogenicity observed in 34 patients with thyrotoxicosis treated with itrumil (iodothiouracil) was not reproducible with equimolar quantities of thiouracil plus potassium iodide given to 10 thyrotoxic patients The mean acinar cell height (MACH) was lower (8 5 μ) in itrumil treated glands than in glands treated with thiouracil plus potassium iodide (10 9 μ) Radioiodine tracer studies in both groups after discontinuance of drug for 15-48 hours showed that when the hyperthyroidism is controlled the 24 hour thyroid uptake is low (13% in itrumil treated patients and 21% in thiouracil plus potassium iodide treated group) If

(2) Am. J M Sc 2 5 178 186 February 1953

the patient has not responded to treatment his uptake is in the hyperthyroid levels (average 65%)

The different modes of action of itrumil and thiouracil plus potassium iodide can be hypothetically explained by assuming that the rapid control of thyrotoxic symptoms accomplished with itrumil is due to an effective selective concentration of this *iodinated molecule in the hyperthyroid* gland Once this iodinated thiouracil is absorbed into the cellular structure of the thyroid gland an inhibition of thyroxin takes place in the cell itself Itrumil simultaneously raises the iodine concentration and inhibits the production or release of the thyroid stimulating hormone from the pituitary Once the production of thyroid stimulating hormone and its local action in the thyroid cell are inhibited or decreased the thyroid gland has an opportunity to be restored to normal histology and normal physiologic conditions

[These observations are in keeping with my own experiences Iodothiouracil (itrumil) has its main value in the preoperative preparation of patients Although it is more effective than iodide they are alike in that some patients do not experience a complete remission in thyrotoxicosis —Ed]

Propylthiouracil and Methimazole Therapy Comparative Experiences Glenn W Irwin Helen D Van Vactor and Max S Norris[3] (Indiana Univ) report results of the use of methimazole in 45 and propylthiouracil in 54 hyperthyroid patients Diagnosis was based on characteristic histories physical examination and laboratory studies

The recommended daily dose of *75 150* mg propylthiouracil was found to be inadequate and 300 mg daily in three equally divided doses was given for small 400 500 mg for moderate and 600 800 mg for large goiters Some patients required extended treatment with 500 800 mg daily before symptoms were controlled and in 9 of the 54 patients response was unsatisfactory In five of these treatment was discontinued because of the slow response in the others a prolonged period was required before control was reached

Methimazole was adminstered in equally divided doses every eight hours 15 mg daily for small 30-45 mg for moderate and 60 mg for large goiters Methimazole was about 10 times more potent than propylthiouracil despite the high dosage of the latter Average time required for control of

(3) J A M A. 149 1637 1640 Ag 30 1952

on for nodular goiter with hyperthyroidism had recurrent symptoms and with these cases excluded the incidence was 2 4% In patients who had recurrent hyperthyroidism when initially seen the incidence of recurrence was 4 7% about twice the incidence after primary operation Recurrence was commonly within three years of operation

In half of the 33 patients with recurrent hyperthyroidism the disease was satisfactorily controlled by iodine medication despite moderate sized remnants in some instances Hyper

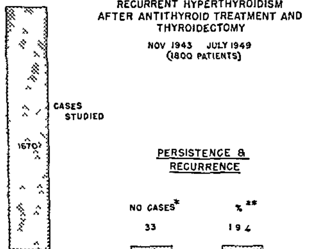


Fig 100 (Courte y f C ttell R B t al J Clin E docrinol 12 1389 1397 O t b 195)

thyroidism was also controlled by antithyroid drugs in two patients by x ray therapy in one and by radioactive iodine in one

A secondary operation because of failure of medical treat ment was necessary in 13 patients There were no deaths and the rate of complications was low The size of the gland and the severity of the symptoms seem to play a part in the development of recurrent hyperthyroidism Recurrent disease was classified as severe hyperthyroidism in more than 80% of the patients The most important factor in avoiding recurrence is the amount of thyroid tissue removed To maintain a low

symptoms with propylthiouracil was 148 6 days and with methimazole 85 6 days a decrease of about 60% Toxic effects were manifested by 9 3% of the patients given propylthiouracil and 6 6% of those given methimazole The incidence of agranulocytosis and fever was almost the same in both groups of patients incidence of urticaria and skin rash was higher in the methimazole group The dosage of methimazole required was about one tenth that of propylthiouracil

No significant conclusions could be drawn concerning the effect of previous iodine therapy on drug action In patients who had received iodine before propylthiouracil therapy the daily dose of the drug and the time required to reach the euthyroid state was less than the averages for the entire group treated with propylthiouracil Five of the patients with unsatisfactory responses to propylthiouracil had received iodine previously iodine therapy was continued in two and discontinued in three patients In the methimazole group there was an increase in the dose requirement and the time interval for control in patients who had received iodine before treatment and in none was iodine therapy continued during methimazole treatment

Size of the goiter and degree of toxicity were the most important factors in the amount of antithyroid drug required and the time necessary for control of symptoms The main objection to propylthiouracil is the length of time and the size of dose required to control symptoms The authors warn that methimazole like other antithyroid drugs should not be used without careful clinical observation

[Of the many antithyroid compounds tested clinically propylthiouracil and methimazole appear to be the best for common usage Methimazole when given in one tenth the propylthiouracil dosage tends to control thyrotoxicosis somewhat more rapidly Considering all reports the incidence of toxic reactions is fairly equal careful study of several thousand patients is necessary to determine accurately the incidence of agranulocytosis —Ed]

Recurrent Hyperthyroidism after Antithyroid Therapy and Thyroidectomy Richard B Cattell A Wade Alford and Elmer C Bartels[4] (Lahey Clinic) state that 1 800 patients treated for hyperthyroidism in 1943-49 received antithyroid therapy followed by subtotal thyroidectomy Of this group 93% were followed for three to eight years Hyperthyroidism recurred (Fig 100) in 33 patients (1 9%) No patient operated

(4) Clin Endocr ol 12 1389 1397 October 1952

of myxedema in the 66 patients who had primary hyperthy roidism (diffuse toxic goiter) and in the 3 patients who had adenomatous goiter with hyperthyroidism Myxedema is more likely to develop in patients who have recurrent primary hyperthyroidism and who require further surgical treatment The likelihood of the occurrence of myxedema after a second thyroid operation is twice as great (11%) as after the initial operation (6%) There was no apparent relation between development of postoperative myxedema and degree of hyper *thyroidism*

The time of onset of myxedema varied widely from almost immediately to five years after operation In about half the patients onset occurred within three months of operation

Pathology reports revealed that 12 patients had strumitis and 3 malignancy Wound infection occurred in two patients and postoperative tetany in five Removal of the parathyroid tissue or disturbed circulation the cause of tetany probably plays a major role in postoperative myxedema

Diagnosis of myxedema in these patients was established on evidence obtained either subjectively or objectively or by *laboratory means (BMR and plasma cholesterol level) The* plasma cholesterol level was considered most helpful the BMR was less informative A retarded growth curve is signifi cant in determining presence of myxedema in children

The daily dose of desiccated thyroid required to control postoperative myxedema varied from 1/8 to 2 gr Myxedema was completely controlled in most cases on daily doses varying from 1/2 to 1 1/2 gr

Radioactive Iodine in Treatment of Hyperthyroidism. E Perry McCullagh[6] (Cleveland Clinic) lists the advantages of I^{131} in treatment of hyperthyroidism (1) In diffuse goiter *more than 10 000 rep can conveniently be placed inside the* thyroid as against only about 2 000 r with x ray or radium (2) Uptake is high in hyperthyroidism when it is needed and when thyroid function is normal is low enough that it is difficult to cause hypothyroidism if a normal gland is treated—the thyroid in Graves disease can concentrate about 10 000 times more I^{131} than any other tissue (3) About 85% of the radioactivity in I^{131} is beta rays which travel 2 mm or less and thus tissues adjacent to the thyroid are not

(6) A I t Med 37 739 744 O t b 1952

incidence radical subtotal thyroidectomy is essential It is best to leave but 2 Gm of tissue on each side in all cases whether glands are small or large

If patients remain symptom free for five years after operation recurrences thereafter will be rare *Antithyroid* drugs have not materially altered the incidence of recurrent hyperthyroidism or the surgical approach to its treatment

[This is the largest reported series of thyrotoxic patients receiving one of the thiouracils preoperatively The incidence of recurrence is low but no different than with the use of iodide preoperatively The incidence of myxedema with the two types of preparation also is similar—approximately 5% —Ed]

Post thyroidectomy Myxedema after Preoperative Use of Antithyroid Drugs Elmer C Bartels[5] (Lahey Clinic) studied postoperative myxedema in 942 hyperthyroid patients aged

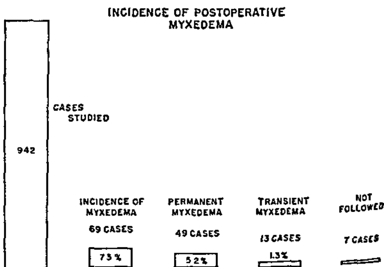


Fig 101 (Courtesy of Bartels E C J Clin Endocrinol 13 95 106 January 1953)

6 68 who received antithyroid drugs until a euthyroid state was attained before thyroidectomy Myxedema developed in 69 patients (7 3%) and in 49 (5 2%) was permanent (Fig 101) These results compare favorably with those reported from the clinic before antithyroid drugs were used There was no sex factor There was a significant difference in development

(5) J Clin Endocrinol 13 95 106 January 1953

There is no method by which the completely effective dose can be calculated Methods of calculation of dosage are currently based on weight of the gland as judged by palpation and percentage uptake of I^{131} by the thyroid Usual dose is between 100 and 200 μg/Gm of thyroid The patient must be carefully followed after the original dose and if in two months there has been no improvement the dose is repeated If there is partial improvement half the original dose is given If the BMR is less than +20% and there is reason to suppose that normality may soon be reached no more treatment is given for another two months

Results have been excellent in 642 patients with Graves disease Only 10% had hypothyroidism (often transient) after treatment One patient had a near crisis which required concentrated treatment At the end of 6 months 98% of the patients were free from hyperthyroidism Only one patient is listed as a failure and the treatment was abandoned in two children in favor of surgery In 2% with recurrences from 20 to 50 weeks after treatment retreatment was as effective as initial treatment

Advantages of I^{131} treatment of Graves disease are no deaths no vocal cord paralysis no chronic tetany almost 100% complete control reduction of thyroid size usually to normal no discomfort no time or income loss no hospitalization no more frequent hyperthyroidism than after surgery fewer recurrences than in other forms of treatment easy treatment of recurrences by I^{131} and the cheapness of the treatment

[This report warrants careful consideration because it covers the largest series yet reported of thyrotoxic patients treated with I^{131} Moreover Dr McCullagh and his colleagues have had extensive experience with the use of antithyroid drugs alone and combined with thyroidectomy —Ed.]

Five Year Experience with Radioactive Iodine in Treatment of Hyperthyroidism D E Clark J H Rule O H Trippel and D A Cofrin[7] (Univ of Chicago) report on 384 hyperthyroid patients treated with radioactive iodine and followed for 6 60 months There were 204 with toxic diffusely enlarged glands and 180 with toxic nodular glands About 75% were over age 40 Each case fulfilled one or more of the following criteria (1) uncomplicated hyperthyroidism in patients over age 40 (2) recurrent or persistent hyperthyroidism after thyroidectomy (3) hyperthyroidism with severe

(7) J A M A 150 1 69 1272 Nov 29 1952

damaged (4) Since I^{131} has a half life of 8 days 99% of the *original strength* is dissipated in 52 days therefore it lasts long enough to be effective and disappears soon enough that too large a dose does not cause excessive damage and too small a dose can readily be corrected (5) In the doses used there is no renal or bladder damage amenorrhea infertility or parathyroid damage (6) Although I^{131} is not suitable for treatment of hyperthyroidism in pregnancy if it is given in early pregnancy the fetus is protected by inability of its thyroid to concentrate radioactivity until after the third month (7) Radioactive iodine can be used in testing thyroid function because the activity is carried by a dose of chemical iodine too small to affect the normal physiology of the gland

Obstacles to use of I^{131} in Graves disease are (1) it is not generally available and (2) its effects may be blocked by iodine In nodular goiter disadvantages are (1) the tendency to slow response to I^{131} and (2) failure to remove the nodules completely

Uptake of I^{131} by the thyroid aids in diagnosis of hyperthyroidism An uptake exceeding normal indicates thyroid hyperactivity Urinary excretion of I^{131} and serum radioactive protein bound iodine content can be measured for diagnostic purposes

Treatment of choice in multinodular goiter is surgery because of the danger of cancer If surgery cannot be performed the hyperthyroidism can be controlled with I^{131} The hyperthyroidism of nodular goiter and that of Graves' disease must be clearly differentiated because in nodular goiter the dose required for control is larger rate of improvement is slower and larger doses may be given with impunity because post treatment myxedema has never been observed in this condition Average dose for 102 patients with hyperthyroidism of nodular goiter was 34 mc as compared with 12 mc. for Graves disease Graves disease was controlled in 2-4 months in most patients whereas nodular goiter took an average of 6½ months

Radioactive iodine is most outstanding in treatment of Graves disease The most evident indication for I^{131} is in recurrent hyperthyroidism after surgery It is also indicated in cardiac patients the aged and those who have a recurrence after antithyroid drugs

There is no method by which the completely effective dose can be calculated Methods of calculation of dosage are currently based on weight of the gland as judged by palpation and percentage uptake of I^{131} by the thyroid Usual dose is between 100 and 200 μg/Gm of thyroid The patient must be carefully followed after the original dose and if in two months there has been no improvement the dose is repeated If there is partial improvement half the original dose is given If the BMR is less than +20% and there is reason to suppose that normality may soon be reached no more treatment is given for another two months

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(7) J A M A 150 1269 1272 Nov 29 1952

cardiovascular or some other concurrent disease (4) failure to respond properly to antithyroid drugs (5) refusal of ur gery or other therapy and (6) presence of severe exophthal mos The coexistence of hyperthyroidism and pregnancy is a contraindication to radioactive iodine therapy

Diagnosis of hyperthyroidism was made on the basis of clinical judgment BMR radioiodine diagnostic studies and protein bound iodine determinations

The average dose of I^{131} given to patients with diffusely enlarged glands was 0 24 mc/Gm estimated thyroid weight and to patients with nodular glands 0 33 mc/Gm (table)

Remissions were obtained in 76 1% of patients with one

MILLICURIES OF I^{131}/GRAM ESTIMATED THYROID WEIGHT

AGE GROUP YR	TYPE O GL Diffuse	Nodul r
10-19	0 14	—
20-29	0 18	0 22
30-39	0 19	0 33
40 49	0 28	0 32
50 59	0 27	0 30
60 69	0 33	0 40
70 79	1 30	0 34
80 89		0 33
Over all	0 24	0 33

or two doses The others except for one patient required from three to seven doses In all 327 patients (85 2%) had satis factory remissions varying degrees of hypothyroidism devel oped in 13 8% and 1% have apparently permanent myxedema There have been no recurrences

Exophthalmos was observed in 114 patients Of 94 ade quately evaluated 19 1% had complete regression and 58 5% showed variable improvement No patient with exophthalmos before I^{131} therapy showed progression There have been no complications of radioiodine therapy except hypothyroidism and three instances of post therapeutic unilateral exophthal mos

These observations show that radioactive iodine is an ac ceptable therapeutic agent in selected cases of hyperthy roidism

Hyperthyroidism—Evaluation of Treatment with Antithy roid Drugs Followed by Subtotal Thyroidectomy On the basis of results in 2 400 patients Elmer C Bartels[8] (Lahey Clinic) states that antithyroid drugs aid greatly in the preoperative

(8) An Int. M d. 7 1123-1134 D mb r 195

treatment of hyperthyroidism They must be administered under careful observation because serious blood changes particularly agranulocytosis are a real danger Patients must be treated individually and no patient should undergo thyroidectomy until a euthyroid state is reached and all evidence of hyperthyroidism and resulting physical depletion are overcome If this is accomplished a low operative mortality is possible—0 2% in this series

Antithyroid drugs can safely be given to pregnant patients with hyperthyroidism if myxedema is avoided pre and post operatively until the time of delivery Normal delivery at term occurred in 21 of the 27 pregnant patients In six the outcome was variable and appeared completely unrelated to antithyroid treatment or thyroidectomy

Postoperative tetany occurred in 3% of patients and was permanent in 1 8% It began on the first to sixth day Transient tetany lasted from five days to four years (average three months) The incidence of tetany was greater in patients who had previously undergone surgery on the thyroid gland In all patients tetany was controlled with powdered calcium lactate alone or in combination with vitamin D

Hyperthyroidism recurred in 33 of 1 670 patients (1 9%) followed by periodic metabolic studies for three to eight years These patients were treated selectively in most of them the disease was controlled either by daily administration of iodine or by a second operation with removal of the recurrent thyroid remnants

Postoperative myxedema occurred in 7 3% of the first 942 patients in 5 2% it was permanent It developed any time up to the fifth postoperative year but usually in the first year and became permanent if thyroid was required after the first year Desiccated thyroid controlled all cases the usual dose being 1½ gr or less

[With the use of the new antithyroid drugs preceding thyrodectomy no change was found in the incidence of recurrence of thyrotoxicosis or the development of myxedema However the operative mortality interval of hospitalization etc. have decreased considerably —Ed]

Effects of Adrenocortical Stimulation on Thyroid Function Clinical Observations in Thyrotoxic Crisis and Hyperthyroidism D Emerick Szilagyi Arthur B McGraw and Nicholas P D Smyth[9] (Henry Ford Hosp) observed the clinical effects of corticotrophin in three cases of severe

(9) Ann S g 136 555 577 O tobe 1952

thyrotoxic crisis in which other measures were unsuccessful and in five cases of hyperthyroidism which had presented unusual difficulties in preoperative preparation Corticotrophin seemed beneficial in thyroid crisis although other medications were given All three patients recovered In hyperthyroidism the clinical course was only moderately or slightly improved however all patients treated preoperatively with corticotrophin and with very inadequate amounts of iodine or with no iodine withstood radical thyroidectomy well

It is postulated that the beneficial effect of corticotrophin in thyrotoxic crisis and on the operative reaction and postoperative recovery of thyrotoxic patients is actuated through the antistress response of the adrenal cortex The establishment of a clinical state of thyrotoxicosis is assumed to be the result of the quasiantagonistic actions of the adrenocortical and thyroid hormones If thyroxin production is high but accompanied by an adequately increased adrenocortical output a state of compensated hyperthyroidism exists If the cause of overproduction of thyroxin is intrathyroidal rather than pituitary in origin in untreated hyperthyroidism the increase in circulating thyroxin is not counterbalanced by a raised cortical output and the stress response balance is thrown out of equilibrium in favor of stress As the cortical response lags behind the increased thyroxin output the state of hyperthyroidism eventually becomes decompensated and the state of thyrotoxic crisis appears Administration of corticotrophin will restore homeostasis by increasing the output of corticoids

Goiter Prevention with Iodized Salt Results of 30 Year Study According to *Brock E Brush and J K Altland*[1] the State Department of Health Michigan has conducted surveys in 1923 1928 1935 and 1951 in four counties to evaluate the effect of iodized salt on the incidence of goiter For 30 years Michigan has conducted an educational program to emphasize the fundamental causes of endemic goiter and has urged the voluntary use of iodized salt The first survey in 1923 showed a definite correlation between the lack of food iodine and the incidence of *simple goiter In the 1928 and 1935 surveys* the decline in goiter was remarkable among those who used iodized salt—an over all reduction of incidence from 38 6 to

(1) J Clin Endocrinol 12 1380-1388 October 1952

8 2% In those who had used the iodized salt the incidence was reduced to 2 and 3% whereas in those who had not the incidence remained at 25 35% In 1951 the incidence of goiter was 1 4% among 53 785 students as against 38 6% among 65 537 students examined in 1924 The results in a typical county (Wexford) are shown in Figure 102

The daily adult requirement of iodine is 0 15 0 30 mg and iodized salt can meet this requirement No ill effects have

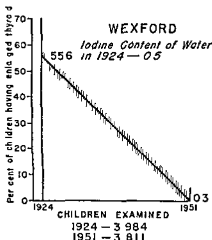


Fig 102 —R lt n typ l ou ty (Cou t y f B h B E nd Altland J K J Cl E doc l 12 1380 1388 Octob 1952)

been noted from the use of iodized salt Salt can be iodized accurately efficiently and inexpensively Toxic nodular and diffuse goiters are less apt to occur when there has been no previous enlargement of the gland as in endemic goiter

[This follow up study on the use of iodine for goiter prophylaxis is most significant Not only has the incidence of goiter been reduced considerably but also thyrotoxicosis and cancer of the thyroid We should be more insistent on the use of this prophylactic agent —Ed]

Diagnosis and Treatment of Thyroiditis with Special Reference to Use of Cortisone and ACTH are discussed by George Crile Jr and R W Schneider In subacute thyroiditis x ray therapy 600 1 000 r relieves symptoms promptly and within a week or two reduces the size and hardness of the thyroid ACTH or cortisone relieves symptoms within 4 hours and in

(2) Cl land Cl Q t 19 219 224 Oct b 1952

48 hours greatly changes the size and consistency of the thyroid Simultaneous x ray therapy prevents recurrences after short courses of hormone therapy

Struma lymphomatosa or lymphoid thyroiditis characterized by a symmetrical firm nodular enlargement of both lobes of the thyroid responds specifically in one or two months to large doses of desiccated thyroid i e. 2 or 3 gr daily X ray is beneficial but unnecessary One patient with no response to either thyroid or x ray therapy experienced immediate relief with administration of cortisone in decreasing doses of 100 mg to 25 mg/day over 11 days Improvement was maintained by simultaneous administration of desiccated thyroid in doses of 1 gr/day for one week 2 gr/day for one week and then 3 gr daily Tenderness of the thyroid disappeared and the gland decreased in size

The diagnosis of thyroiditis may be confirmed by needle biopsy and surgery avoided by following the treatment outlined

Thyroiditis is discussed by George Crile Jr [3] (Cleveland) The three main types are Riedel s struma struma lymphomatosa and subacute or giant cell thyroiditis Riedel s struma is a rare diffuse fibrosis of the whole cervical region simulating inoperable cancer and often necessitating surgical decompression of the trachea

The most common type is subacute thyroiditis which varies in manifestations from a sudden onset with severe pain fever and prostration to a chronic process with sore throat ear or jaw pain and daily fever unrelieved by antibiotics The chronic process may simulate adenoma or carcinoma of the thyroid globus hystericus or fever of unknown origin The entire gland usually is diffusely enlarged hard and slightly tender X ray therapy (600 800 r) usually causes prompt and permanent remission of signs and symptoms Administration of cortisone or ACTH produces immediate but short lived remissions

Struma lymphomatosa diffusely involve the entire gland with a nodular enlargement resembling nodular nontoxic goiter but its characteristic firm hard rubbery consistency along with a hypothyroid tendency differentiates it from

(3) Ann I t. Med. 37 519 5 4 Septembe 1952

nodular goiter Biopsy with the Silverman needle confirms the diagnosis

Lymphoid thyroiditis—possibly an early struma lymphomatosa—occurs commonly in women aged 20-40 It causes a progressive smooth firm symmetrical thyroid enlargement and is accompanied by low BMR and clinical evidence of mild hypothyroidism Both lymphoid thyroiditis and some cases of struma lymphomatosa respond specifically to treatment with desiccated thyroid in doses of 3 gr daily X ray therapy may also be of value Cortisone or ACTH may cause transitory remissions Thyroidectomy is rarely indicated

ADRENAL GLANDS

Progress has been made in the treatment of hyperfunctioning lesions of the adrenals (1) surgery for the tumors and for bilateral hyperplasia associated with pronounced Cushing s disease and (2) cortisone for adrenogenital syndrome due to bilateral hyperplasia. Nor epinephrine has proved to be of great value in many patients with shock The epinephrine test for pituitary and adrenal function has been shown to be very unreliable. Tests of adrenal function using ACTH intravenously are among the best. Determinations of 17 hydroxysteroids in the blood or urine have helped enormously in evaluating adrenal function and the fate of its chief steroid Compound F (hydrocortisone) but these tests are too complicated to use routinely The water load test for adrenal insufficiency has been further simplified and is quite practical —Ed

Management of Certain Hyperfunctioning Lesions of Adrenal Cortex and Medulla Randall G Sprague Walter F Kvale and James T Priestley[4] (Mayo Clinic) state that patients with Cushing s syndrome have a distinctive habitus characterized by obesity or abnormal distribution of fat and wasting of muscle so that the face neck and trunk appear obese and the extremities thin They have muscular weakness hypertension osteoporosis amenorrhea or impotence hirsutism and acne of some degree in the absence of other evidences of virilization thin skin with distinctive purplish striations and a tendency to ecchymosis and a cervicodorsal fat pad Some or all of the following conditions should be present lymphopenia eosinopenia alkaline urine hypochloremic hypopotassemic alkalosis and impairment of carbohydrate tolerance as demonstrated by elevated fasting blood sugar levels

(4) J.A.M.A 151 6 9 639 Feb 1 1953

or abnormalities of the glucose tolerance test Excretion of 17 ketosteroids may be low normal or increased The syndrome may be due to either a functioning tumor of the adrenal cortex or to adrenal cortical hyperplasia It is not possible to make an accurate diagnosis of tumor or hyperplasia and surgery is indicated in all cases

Preoperative preparation consists of intramuscular administration of 200 mg cortisone acetate 48 hours before operation 24 hours before operation and also on the morning of the day of operation Postoperatively there is almost always some adrenal insufficiency and 100 mg cortisone acetate is given intramuscularly on each of the first two days after operation 50 mg on each of the next two days and 25 mg on each of the two following days A liter of isotonic sodium chloride solution is given intravenously daily on each of the first four days after surgery

Posterolumbar incisions are made at operation If a tumor is found in the first adrenal gland exposed the tumor is removed and nothing further is done If an atrophic gland is encountered the incision is closed after biopsy and the opposite adrenal is then exposed with the reasonable expectation of finding a tumor which is then removed If neither a tumor nor an atrophic gland is found in the first gland exposed subtotal (85 90%) resection of the first gland is performed Every effort is made to preserve an adequate blood supply for the remaining portion of glandular tissue The opposite adrenal gland is then exposed and total adrenalectomy is performed on this side

After removal of an adrenal cortical tumor remission of the signs and symptoms of the disease gradually ensues and recovery in most cases is essentially complete If the tumor is malignant and recurs the syndrome may again develop

Subtotal adrenalectomy was performed in 49 cases and total adrenalectomy was performed in 1 case for adrenal cortical hyperfunction There were 11 males and 39 females aged 13 58 The excretion of 17 ketosteroids varied over a wide range but the excretion of corticosteroids was higher than normal in most cases The weight of the glands removed varied from 3 7 to 26 5 Gm and most were over 6 0 Gm which is considered the normal weight of the gland It is

necessary to remove probably 90% or more of the gland to insure remission There were six hospital deaths

Of the 41 surviving patients in whom subtotal (40 patients) or total (1 patient) adrenalectomy was completed all but 1 were in remission (Fig 103) Some patients needed more than one operation because of incomplete remission following the first operation Replacement therapy for adrenal insufficiency was necessary in 20 patients Treatment is with cortisone acetate alone or cortisone acetate plus desoxycorticosterone acetate A postoperative reaction occurred in almost



F g 103—C h g y d m ca d by d n co t l hyp rpl *A* b f p t *B* x m ths ft tot l m l f n ad en l gland d exte v bt t l m l f th th (Cou t y f Sp gu R G *t al* J A M.A 151 629 639 F b 21 1953)

all cases when cortisone was withdrawn The resumption of cortisone corrected the reaction Of 44 patients who had hypertension before surgery 28 were normal after surgery The glucose tolerance test usually improved postoperatively Cutaneous melanosis of the type seen in Addison s disease occurred postoperatively in 12 patients The 17 ketosteroid excretion usually fell to normal after surgery if enough adrenal was removed

The most frequently encountered surgical lesion of the adrenal medulla is a pheochromocytoma or tumor composed of chromaffin tissue Of 25 patients with pheochromocytoma 14 had intermittent attacks of hypertension and 11 had sustained hypertension Half of those with paroxysmal hypertension were men of age 26 59 Symptoms included headache

palpitation tremor and perspiration Eight of the 11 with sustained hypertension were women of age 18-48 Pheochromocytoma may be difficult to diagnose clinically and much help has been derived from various pharmacologic tests Histamine has been the most valuable in the diagnosis of pheochromocytoma causing paroxysmal hypertension whereas piperoxan hydrochloride and regitine* have been the most useful drugs in the diagnosis of pheochromocytoma causing sustained hypertension In 40 tests performed in patients with paroxysmal hypertension the results were negative in 16 and in 30 tests performed in those with sustained hypertension results were negative in 9

Because of the possibility of abdominal tumors the transabdominal surgical approach is usually advised If a pheochromocytoma is encountered the surgeon should palpate it as little as possible in order to prevent severe hypertension If the tumor is benign uninvolved adrenal tissue may be preserved if an adequate blood supply to this remnant can be maintained If bilateral tumors are present it is especially important to preserve some adrenal cortical tissue if possible Hypertension during surgery should be controlled with regitine* or piperoxan and epinephrine or arterenol should be used to combat the hypotension that occurs when the tumor is removed After surgery the patient should be carefully watched for changes in blood pressure

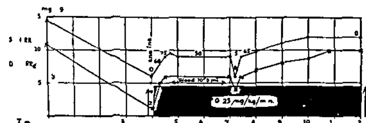
Sixteen tumors weighing 10 575 Gm were removed from the 14 patients with paroxysmal functioning tumors and 18 tumors weighing 50-355 Gm were removed from the 11 patients with sustained hypertension Four patients had malignant tumors and four had bilateral tumors Results were gratifying in almost all cases

[The conclusions are based on many years observations of apparently the largest group of patients with hyperadrenalism studied by any clinic. However it should be emphasized that patients with full blown Cushing's syndrome are rare These patients should be carefully differentiated from a vast number who have hypertension obesity diabetes hypomenorrhea etc which in composite form is quite different in pathologic physiology course and in type of therapy required —Ed]

Studies on Clinical Use of Nor adrenaline In the treatment of acute irreversible shock caused by hematogenic disease hemorrhage anesthesia or trauma Aimo Pekkarinen and Lauri Aro[5] (Helsinki) have used intravenous administration

(5) A n chir 1 gy aet F nniae 41 69 85 1952

of nor epinephrine in addition to other therapy (oxygen transfusions of whole blood plasma and other fluids Trendelenburg s position and stimulants) Nor epinephrine acts chiefly on the peripheral sympathetic nerves and has a swift and transient action when given intravenously Intravenous infusion permits easy regulation of dosage During infusion nor epinephrine causes a rise in both systolic and diastolic blood pressure there is no significant change in pulse pressure The rise in systolic and diastolic pressure is due to peripheral vasoconstriction in the capillary areas e g in regions of skin splanchnic organs and musculature The coronary arteries are distended When the capillary net contracts the



F g 104 —Hem t g hock ft pl t my f p my l phthis Bl k ea d t p ph f F ll n blood p to 60/40 ft th hou f p ph w du t l gg g f n dl (Cou t y f P kk n en A a d A L A h t gy a F 41 69 85 1952)

heart rate falls by reflex action in normal subjects but the heart rate usually does not change in patients in shock Blood sugar content is slightly raised

Nor epinephrine as a strong vasoconstrictor is a potent and suitable agent in the treatment of shock due to circulatory collapse It can raise blood pressure in a very short time (Fig 104) The systolic blood pressure rises as a rule within a few minutes from the low levels of 40-60 mm Hg to normal There is no effect on secretion of urine

Nor epinephrine infusion (4 mg or more nor epinephrine to a liter of physiologic saline 5% glucose or aminosol® glucose) can be maintained for 4½ 20 hours with the rate of 0 05 0 23 μg /kg /min the total amount of nor epinephrine ranging from 2 mg to 8 mg The drip infusion must always be kept under close observation to prevent excessive rise in blood pressure or excessive fall if the supply of fluid containing nor epinephrine slows down or stops The concentration

palpitation tremor and perspiration Eight of the 11 with sustained hypertension were women of age 18-48 Pheochromocytoma may be difficult to diagnose clinically and much help has been derived from various pharmacologic tests Histamine has been the most valuable in the diagnosis of pheochromocytoma causing paroxysmal hypertension whereas piperoxan hydrochloride and regitine* have been the most useful drugs in the diagnosis of pheochromocytoma causing sustained hypertension In 40 tests performed in patients with paroxysmal hypertension the results were negative in 16 and in 30 tests performed in those with sustained hypertension results were negative in 9

Because of the possibility of abdominal tumors the transabdominal surgical approach is usually advised If a pheochromocytoma is encountered the surgeon should palpate it as little as possible in order to prevent severe hypertension If the tumor is benign uninvolved adrenal tissue may be preserved if an adequate blood supply to this remnant can be maintained If bilateral tumors are present it is especially important to preserve some adrenal cortical tissue if possible Hypertension during surgery should be controlled with regitine* or piperoxan and epinephrine or arterenol should be used to combat the hypotension that occurs when the tumor is removed After surgery the patient should be carefully watched for changes in blood pressure

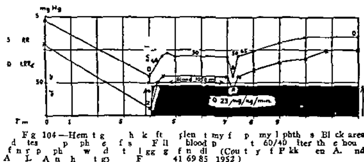
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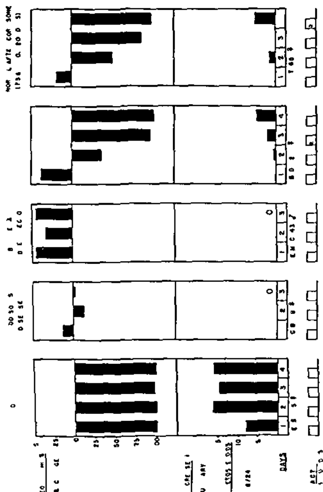
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(5) Ann chi et gyn ec. Fe iae 41 69 85 1952



renocortical response increased with the amount of ACTH used up to a critical dosage above which no further response was elicited In eight subjects with normal adrenal function this critical dosage was 20 I U of ACTH or less (Fig 105) A maximal rise in 17 ketosteroids in response to such a stimulus suggests that the steroid discharging action of ACTH on

of the solution should be adjusted so that there is no need to *introduce too much fluid with the nor epinephrine Infusion* can be continued over several days if necessary

[My own experience has demonstrated that nor epinephrine has been of great value in many types of hypotensive crisis —Ed.]

Use of Intravenous ACTH Study in Quantitative Ad **renocortical Stimulation.** Albert E Renold Dalton Jenkins Peter H Forsham and George W Thorn[6] (Harvard Med School) used eosinopenia and rise in urinary 17 ketosteroid excretion as indexes of the degree of adrenocortical activation

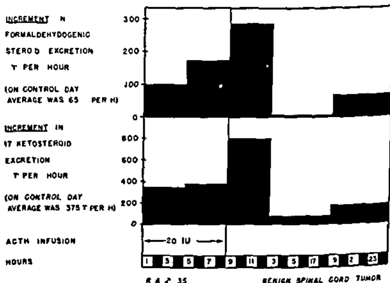


Fig 105 —Ch ges u a y te d ex t n d i g a d afte t a e o s inf n of 20 I U of ACTH o ght ho s (Co rt y of Re ld A E *et al* J Cl n End c nol 12 63 797 J ly 1952)

Intravenous administration insures the most direct contact of the hormone with the target gland and the use of con tinuous infusion makes constant controlled stimulation possi ble The fall in circulating eosinophils served as a simple in dicator of the rise in 11 17-oxygenated adrenal steroids The increase in urinary 17 ketosteroids which has been assumed to represent an over all measure of adrenal cortical response was found to be proportional to the logarithm of the dosage of ACTH used For an eight hour period of infusion the ad

(6) J Clin. Endocrinol. *12 763-797 July 1952*

daily infusions of ACTH will tend to reveal the potential adrenal cortical reserve which is composed of the total syn thetic capacity as well as of the degree of functional and anatomic hypertrophy of which any given pair of adrenal cortexes might be capable Four distinct groups appeared among subjects given repeated daily infusions of ACTH In one group 17 ketosteroid excretion reached a maximum in two to three days In a second group the rise in 17 ketosteroids occurred in two stages the second rise being coincident with clinical improvement of widespread disease In a third group

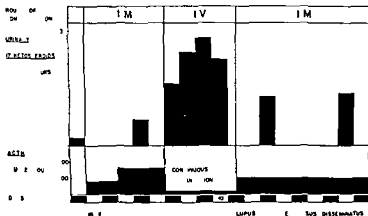


Fig 107—Compa son [illegible] ACTH (Court y f Ren ld A E *et al* J Cl Endoc ol 12 763-797 J ly 1952)

the excretion of 17 ketosteroids rose progressively through out treatment and in the fourth group there was only a small rise of 17 ketosteroids in the absence of clinical signs of ad renal insufficiency

Resistance to ACTH administered intramuscularly was studied This is due to increased fixation and destruction of ACTH at the site of injection Resistant subjects were found to respond normally to intravenous administration of the same material (Fig 107)

The intravenous infusion of ACTH lends itself to human assay with changes in 17 ketosteroid excretion serving as a measure of ACTH activity As a form of therapy the intra venous administration of ACTH offers the advantages of

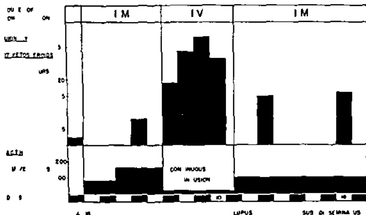
the adrenal cortex is limited It is conjectured that the degree of adrenal cortical activation produced by ACTH depends on the surface area of the adrenal cortex available for ACTH action *maximal stimulation being obtained when all the available sites are being affected by ACTH*

When the dose of 20 I U of ACTH was continuously administered for periods varying from 30 seconds to 48 hours a linear increase in adrenal cortical stimulation occurred with increasing duration of administration This suggests a rapid inactivation of excess ACTH which appears to vary with the nature of the ACTH preparation used The time response relationship for ACTH suggests that only a fraction of a rapidly administered hormone is utilized for adrenal cortical activation A varying portion of the hormone is apparently inactivated and greater impurity of the material used results in more inactivation When ACTH is administered by slow intravenous drip fixation by the adrenal occurs continuously and before inactivation by other tissues has taken place to any significant extent

The use of the eight hour infusion of 20 I U of ACTH intravenously is a good test for the evaluation of the immediate adrenal cortical reserve It is more quantitative than the intramuscular tests in which excessive local tissue inactivation has been found with certain types of ACTH The single eight hour intravenous test does not differentiate readily between primary adrenal insufficiency and that due to anterior pituitary failure However if the test is run for three consecutive days a gradual increase in response suggests pituitary insufficiency *whereas failure denotes primary adrenal* insufficiency In cases of adrenal cortical involution (Fig 106) the much greater sensitivity of the eosinophils as opposed to the 17 ketosteroid excretion is clearly indicated Whereas there is little danger of anaphylaxis in patients with normal adrenal cortical reserve febrile reactions chills and malaise may occasionally be encountered in those with poor adrenal response *These manifestations are usually mild* and *it is anticipated* that they will be less frequent with the increasing purity of *available preparations*

Whereas a single infusion of ACTH will reveal the immediate adrenal reserve composed presumably of pre existing *stored hormone and direct hormonal precursors* repeated

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death seemed to be an important factor in the three patients in whom eosinopenia did not develop The eosinophil level had not had enough time to respond fully to the stress of dying The count rose from low levels to normal in the 12 patients who recovered from the moribund state

This study indicates that the adrenal cortex does not fail during prolonged stress but continues to show hyperactivity up to the very moment of death Supportive therapy with corti cal substances is therefore not indicated in terminal states

The eosinophil count seems to be of only limited prog nostic value in moribund cases since changes usually accompany or lag behind rather than precede the clinical findings However a rising eosinophil level in a patient who continues to appear moribund is a good prognostic sign

Influence of ACTH on Sodium and Potassium Concen tration of Human Mixed Saliva B Grad[9] (McGill Univ) determined the sodium and potassium concentrations in speci mens of unstimulated saliva collected from four patients be fore meals and at bedtime for several days before during and after ACTH administration ACTH significantly reduced the sodium potassium ratio in 15 of 16 experiments the effect being similar in specimens collected at different times of the day The sodium concentration decreased in all 16 experiments and the potassium concentration increased in 13 The response of the sodium and potassium concentrations of saliva to ACTH was similar to and as sensitive as that of sweat or as that of the daily amounts of sodium and potassium in the urine The day to day variation in sodium and especially in potassium concentration of unstimulated saliva collected at the same time of day was relatively slight even though the subjects were on an unrestricted intake of sodium and potas sium The effect of ACTH on sodium and potassium metab olism can be more easily studied in the saliva because of the ease of collection and its ready availability

Effect of Adrenocorticotrophic Hormone (ACTH) on Serum Amylase Activity and Carbohydrate Metabolism C L Tribby[1] (St Vincent s Hosp Bridgeport Conn) found that 90% of 20 patients with rheumatoid arthritis had significantly elevated serum amylase values 24 hours after intramuscular injection of 40 mg ACTH Carbohydrate metabolism as re

(9) J Cl E doc l 12 08-718 J e, 1952
(1) Am J Cl P th 22 855 859 S ptember 1952

economy and reproducibility and the disadvantage of many hours of immobilization

Comparison of Eosinophil and Circulating 17 Hydroxy corticosteroid Responses to Epinephrine and ACTH Vincent C Kelley Robert S Ely Richard B Raile and Patrick F Bray[7] (Univ of Utah) measured the circulating plasma concentration of 17 hydroxycorticosteroids and compared the effects of 0 01 mg epinephrine/kg and of 25 I U ACTH on the levels of these steroids and of eosinophils in normal children and children with various disorders

In general after injection of ACTH there was adequate response of both eosinophils and circulating 17 hydroxycorticosteroid plasma concentration a reduction of the former and an elevation of the latter However some patients exhibited satisfactory eosinopenia without concomitant increase in circulating 17 hydroxycorticosteroid concentration, whereas others had no eosinopenic response despite adequate elevations of 17 hydroxycorticosteroids The question is raised whether the eosinopenic response to ACTH need be mediated by an increased secretion of 17 hydroxycorticosteroids by the adrenal cortex

In contrast to the generally adequate response of 17 hydroxycorticosteroids to ACTH usually no elevation of these steroids occurs in response to epinephrine despite adequate eosinopenia There is a strong suggestion that the eosinopenic response to epinephrine is not mediated by an increased circulating concentration of 17 hydroxycorticosteroids

[These observations have distinctly practical significance. The eosinopenic response does not always correlate well with the steroid response, nor with other characteristics of adrenal or pituitary function The epinephrine test is not satisfactory —Ed]

Adrenal Cortical Function at Death as Measured by Level of Circulating Eosinophils Paul B Jennings[8] (Atlanta Ga) followed 50 moribund patients with a variety of diseases by means of serial eosinophil counts until the time of their death Results were compared with counts of 54 controls and of 12 patients who were moribund but recovered Of the 54 controls only 10% had fewer than 30 eosinophils/cu mm In 94% of the patients who died the eosinophil count fell to zero or close to zero and remained so until death Suddenness of

(7) Proc Soc. E pe B 1 & M d 81 611 614 D mber 195
(8) D t M J 1 10 5-10 8 M 17 195

Protein hypercatabolism can be associated with ulcer penetration and perforation impaired wound healing diminished localization of infection muscle weakness osteoporosis and diabetogenesis and a high protein diet may eliminate these effects Sodium retention may be responsible for edema hypertension and perhaps mental derangement a salt restricting diet may prevent these complications Potassium depletion may be associated with muscle weakness and perhaps insulin resistance and mental derangement potassium should be supplemented in the diet

The production or metabolism or both of adrenal steroids is modified in a major way by diet A study of 14 patients with rheumatoid arthritis and other diseases who had been maintained on ACTH or cortisone or both indicated that sodium intake of all patients receiving these hormones should be limited to not more than 1 Gm/day A high protein diet 100 200 Gm/day is essential Potassium supplementation of 4-12 Gm/day is essential in all with good renal function Incomplete metabolic studies also reveal that a diet composed of protein and fat as the only sources of calories is compatible with a maximal therapeutic response and a minimal occurrence of untoward effects

Inhibition of Catabolic Effect of Adrenocorticotrophic Hormone (ACTH) in Rats by Diet High in Potassium Chloride John E Whitney and Leslie L Bennett[3] (Univ of California) carried out four series of metabolic experiments in which groups of five normal plateaued female rats were maintained on a stock diet a diet high in KCl or a diet high in NaCl The food intake was constant and urine specimens were collected daily for total nitrogen determination All animals were given ACTH in increasingly large doses until a significant increase in urinary nitrogen was observed in the animals on the controlled diet A similar increase in urinary nitrogen was observed in the animals on the high NaCl diet but there was no increase in those on the high KCl diet There was no difference in the weight and histologic appearance of the adrenals of the animals receiving ACTH whether they were on the control or the high KCl diet Results therefore indicate that the high KCl diet does not inhibit stimulation of the adrenals by ACTH in normal female rats but that

(3) E doc logy 50 657 663 J ne 1952

flected by the glucose tolerance test was significantly decreased in 60% 24 hours after therapeutic doses of ACTH The typical decreased tolerance curve was similar to the classic curve of diabetes mellitus

The rationale for disturbed carbohydrate metabolism after administration of ACTH is based on the theory that in effect ACTH antagonizes insulin The hormone tends to reduce carbohydrate utilization and to stimulate gluconeogenesis which results in hyperglycemia and an increased demand for insulin In most patients the pancreas compensates for this deficiency by secreting additional insulin Therefore some patients may experience a period of relative hypoglycemia as a consequence of persistent insulin overproduction when ACTH or cortisone therapy is withdrawn However if the functional reserve of the pancreas is inadequate to meet an increased need for insulin patients may become diabetic Probably insulin antagonism by ACTH is not the only factor involved as experimental diabetes produced by ACTH is relatively insulin resistant

The close correlation between elevated amylase activity and a diabetic type of glucose tolerance curve after ACTH therapy suggests that serum amylase also reflects impaired carbohydrate metabolism

[Although the full significance of the increased amylase activity is not known it is important to know that it does occur particularly since the test is used for diagnosis of pancreatic disease —Ed]

Dietary Modification of Metabolic and Clinical Effects of ACTH and Cortisone Laurance W Kinsell John W Partridge Lenore Boling and Sheldon Margen[2] (Oakland Calif) state that some of the undesirable effects of prolonged administration of ACTH and cortisone can be modified by diet Among the clinical effects are edema and hypertension masking of symptoms and signs of infection decreased localization of infectious processes diabetogenesis perforation of gastrointestinal ulcerations precipitation of psychoses muscle weakness osteoporosis hirsutism loss of head hair acne pigmentation actual Cushing's syndrome and impaired wound healing Undesirable metabolic effects are protein catabolism Na and water retention K loss derangement of carbohydrate metabolism Ca and PO_4 depletion and depletion of other essential constituents of protoplasm

(2) A n I t Med. 37 921 929 N n be 1952

ical picture similar to Cushing s syndrome The degree of Cushing s syndrome produced is dependent on the size of dose and on duration of treatment In short term treatment side effects are of little importance and during treatment of potentially lethal diseases their importance is negated by the possibly fatal outcome When the disease is seldom lethal their importance is great and the dose of hormone must be kept

RESPONSIVE SYNDROMES CLASSIFIED ACCORDING TO COURSE AND PROGNOSIS

Acute			Th mbo yt p c P pu
			H molyt A mu
			A te G t
			P ll n A thm
			U t c
			F gn P t l R a t
			P lh R t
			E f l t D rm tit D t G ld
			Acute I t d U t
			Rhe m t c F
Ch nl	Pot tially F t l		L p E ythem t D n t
			Fe t t Nod a
			P mph gu
	N F t l	P gr s v	Ll c t Col tis
			R gi l E t t
			I lm y Be yll is
			S d
			E ly Rh m t d A th t s
			Ch A thm
			U t
		St t c	*B t t Rl m t d Arth tis*
			Ch A thm

as low as feasible to achieve some benefit Specific side effects that are troublesome are masking of common inflammations reactivation of infections development of peptic ulcers and progression of osteoporosis Congestive failure carbohydrate intolerance hypokalemia and development of hypertension have not presented much difficulty

Side effects can be managed by watching the patient s weight and restricting sodium intake Mercurial diuretics may be used Diet restriction of carbohydrate may be necessary for glycosuria Withdrawal of the hormones is likely to be hazardous the original syndrome may be worse after the hormone is stopped Indications for termination of hormone therapy are severe manifestations of Cushing s syndrome

it inhibits the increase in nitrogen excretion produced by this hormone

[Not only this study but others have shown that large doses of potassium antagonize certain actions of adrenal steroid One significant implication is that although large doses of potassium will give protection against some of the ill effects of ACTH there is a possibility that they also might interfere with some of the desired effects of the hormone. —Ed]

Corticotrophin, Cortisone and Related Steroids in Clinical Medicine Practical Considerations Charles Ragan[4] (Columbia Univ) states that it is necessary to understand the nature course and prognosis of a disease before a patient is treated with these hormones The action of the hormones is to decelerate the response of the host to various forms of noxious stimuli—mechanical chemical infectious those resulting from sensitization or those resulting from tumor growth Syndromes responsive to the hormones are classified according to course and prognosis in the table

The aim of hormone therapy in acute cyclic or self limited disorders is to suppress the response of the host only until the noxious stimulus is removed or its action is spontaneously dissipated The use of hormones in rheumatic fever is limited to patients with severe disease who have failed to respond to salicylates It is unlikely that rheumatic heart disease can be prevented by treatment of rheumatic fever The aims of treatment in the sustained therapy of chronic disease vary with the type of disease under treatment cure is rarely possible and the hormones only control symptoms In potentially fatal syndromes the hormones can be given in overdoses in the hope of obtaining some palliation In chronic progressive diseases such as early progressive rheumatoid arthritis hormones can be given in the hope of slowing down the progression of the disease and other methods of treatment must also be used In chronic static diseases some palliation can be expected from the hormones

In chronic diseases hormone therapy must be sustained and its cost must be considered The activity of the disease apparently determines the dosage of hormone required for control with greater activity more hormone is necessary There is also a direct relation between size of dose and side effects Some hyperadrenocorticalism is required to produce an anti inflammatory hormonal action which leads to a clin

(4) Bull New York Acad. Med. 29 355 3 6 M y 1953

with sodium content limited to 500 mg daily All but two received antianemic medication There were few complications to therapy

Within one to three days there was striking clinical improvement in five patients *gradual but limited improvement* in two and no improvement in one who had mostly hematologic manifestations of the disease There was an increase in



F g 108 (l ft) —P t ent t t t f ACTH th py tt c l r al w th cce(ted t m g m H w ght t th t m w 115¼ lb. wh h p t d l f 64½ lb f m h h gh t w ght.
F g 109 (ght) —S m p t t f m th l t ft 77 d y f t ous t fm t w th t so H w ght w 145 lb a d h h d compl em n.
(C rte y f Col he H t l Ann I t Med. 38 554 567 M h 1953)

well being and an increase in activity and alertness Increase *in appetite and food intake was reflected in a gain of body* weight (Figs 108 and 109) Diarrhea disappeared in one to two days with one exception and stools frequently appeared to have a normal consistency Steatorrhea was present throughout treatment but was diminished Hematologic findings were unchanged but all who received antianemic therapy eventually had a sustained correction of their anemia In *some instances there was improvement of serum albumin*

including overwhelming infections which cannot be controlled by antibiotics all tuberculous infections or ones suspected of being tuberculous bleeding peptic ulcers resistant diabetes not readily controlled by diet and insulin major thrombo-embolic phenomena congestive heart failure refractory to the usual measures of treatment severe mental disturbances and abdominal crises such as suspected perforation of a viscus or peritoneal infection Therapy should not be terminated solely because of the appearance of stigmas of Cushing's syndrome or because of mild congestive failure minor infections hypo kalemia correctable by potassium orally mild glycosuria con trolled by diet or development of mild hypertension

The three available hormones are cortisone acetate cor ticotrophin and hydrocortisone acetate (compound F) For all practical purposes cortisone and compound F are similar when given systemically Cortisone orally is the simplest form of therapy Cortisone and corticotrophin can be given intra muscularly Corticotrophin should be given for a few days when cortisone is being withdrawn Compound F can be given intra articularly

[In the light of present information hydrocortisone given orally or intravenously promises to be the most frequently used form of adrenal cortical therapy —Ed]

Management of Intractable Sprue with Cortisone and Adrenocorticotrophin (ACTH) Henry Colcher Stanley R Drachman and David Adlersberg[5] (Mount Sinai Hosp New York City) report on eight patients four men and four women aged 28 72 with primary sprue One patient had the tropical form The most prominent symptoms and signs were diarrhea steatorrhea weight loss weakness anemia polyavitaminosis hypocalcemia hypoproteinemia tetany and osteoporosis Duration of symptoms was 1 20 years and all but one patient had been resistant to conventional sprue therapy

A total of 13 courses of cortisone or 8 courses of ACTH or both was given to the patients The initial dose of ACTH was usually 100 mg daily intramuscularly and the initial dose of cortisone was 100 mg daily orally or intramuscularly The dose of each was usually reduced by 12 5 25 mg decre ments at weekly or biweekly intervals The duration of corti sone treatment varied from 5 to 155 days and that of ACTH ranged from 5 to 35 days With two exceptions all the pa tients were given a low fat high protein high calorie diet

(5) A n I t M d 38 554 567 M h 1953

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F g 109 (ght) —S m p t ent f m th ı t ft 7 d y f contı ou t e tment w th rt so H w ght w 145 lb d h had compl em on.
(Court y f C l b H t al An I t Med 38 554 567 M ch 1953)

well being and an increase in activity and alertness Increase in appetite and food intake was reflected in a gain of body weight (Figs 108 and 109) Diarrhea disappeared in one to two days with one exception and stools frequently appeared to have a normal consistency Steatorrhea was present throughout treatment but was diminished Hematologic findings were unchanged but all who received antianemic therapy eventually had a sustained correction of their anemia In some instances there was improvement of serum albumin

serum calcium roentgenologic findings in the small intestine and content of fat in the stools

Multiple courses of treatment with these hormones in the same patient resulted each time in clinical improvement of essentially the same degree in the same time interval and on approximately the same dose No instance of resistance to this form of therapy had developed

Clinical relapses occurred one to five weeks after cessation of hormonal therapy It was therefore found advisable to maintain therapy resistant sprue patients on minimal doses of cortisone or ACTH compatible with the regression of their symptoms

[The beneficial effects of adrenal cortical therapy obtained in these patients are in keeping with the observation of many other investigators —Ed]

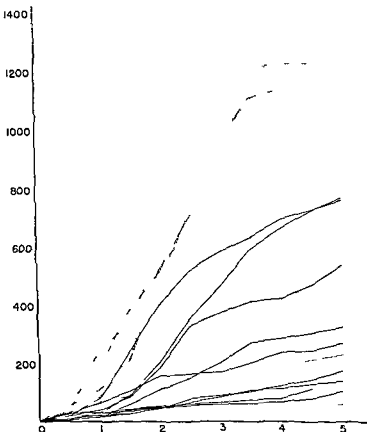
Secretion of Salt Retaining Hormone by Mammalian Adrenal Cortex. S A Simpson J F Tait and I E Bush[7] present evidence that suggests that both the isolated perfused adrenal and the adrenal in vivo of two mammalian species the monkey and the dog can secrete a highly potent substance which is extremely active in its effect on the urinary Na^{24} K^{42} ratio of adrenalectomized rats The substance is similar to if not identical with that previously obtained from extract of adrenal glands

The isolated adrenal of a rhesus monkey was perfused with blood and a blood extract fractionated by paper chromatography Blood was collected from the adrenal vein of a dog and a blood extract fractionated by paper chromatography The chromatograms were then assayed for mineral activity The activity of the cortisone region of the dog blood chromatogram was equivalent to 56 μg desoxycortone whereas only 15 μg cortisone was determined chemically thus indicating the presence of an active mineralocorticoid Similar findings were present in the monkey blood chromatogram The cortisone region of the chromatogram was acetylated and considerable activity was found after hydrolysis that was not due to cortisone

The hormone demonstrated which can be reasonably described as a mineralocorticoid is secreted by the adrenal into the blood stream and is physiologically significant It can be separated from the cortical hormones only by paper chromatography

(7) L n t 2 226 2 7 Aug 2 195

Simplified Water Loading Test for Diagnosis of Addison s Disease Louis J Soffer and J Lester Gabrilove[6] (Mount Sinai Hosp New York City) present a simplified modification of the Robinson Power Kepler water diuresis test for the diagnosis of Addison s disease The fasting patient voids at 8 a m and the urine is discarded He then drinks 1 500 cc tap water



F g 110 —C m l t l m ted fi h ft al g t o f 1 500 t D hed l d te n rmal bj t l d l pat ent w th Add d d dott d) p t ent w th hyp p t t m (L tesy of S ff L J d G b lov J L M t b l m 1 504 510 N mbe 1952)

(6) M t b l m 1 504 510 N mbe 1952

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Lancet 2 336 3 7 Aug 195

tuted salicylic acids 9 produced like SAL a depletion of ascorbic acid The two exceptions were p hydroxysalicylic and p aminosalicylic acid Salicyluric acid and gentisic acid had a much weaker action on the adrenals than SAL owing to their rapid excretion from the body

These experiments indicate that the presence of an intact anterior pituitary is necessary for SAL to reduce the adrenal ascorbic acid content Results with the other acids demonstrate that this action is not due to general stress Results with molecular variants indicate a specific effect of a characteristic chemical structure of which one example is the salicylic acid configuration

It is not known if the effect observed is the result of increased production or of mobilization of stored reserves of ACTH or if the pituitary is the primary target of the action of SAL or is only secondarily stimulated following a primary effect on some other receptor such as the hypothalamus

[The results of this and allied studies suggest that one beneficial action of salicylate therapy might be its capacity to increase ACTH production —Ed]

PITUITARY GLAND

Large Roentgen Doses in Acromegaly Svend C Johnsen[9] (Copenhagen) states that intensive roentgen irradiation of the pituitary can arrest the progression of the disease In 23 cases of acromegaly the pituitary was irradiated in doses which were considerably larger than those previously employed The intensive roentgen irradiation completely inactivated the acromegaly so that the enlargement of the soft parts subsided defects of the field of vision disappeared and the patients recovered their full capacity for work in all probability with prospects of a normal life span These excellent results were in marked contrast with the usual fatal course of acromegaly

In most of the 11 men and 12 women the disease had its onset at age 20 50 Six patients died most of them of causes not connected with acromegaly

Headache which may have been caused by irreversible changes in the growth of the skull persisted in some cases after unquestionable inactivation of the disorder Hypermetabolism in acromegaly is of unknown pathogenesis and

(9) Acta m d ca d na 144 40 61 1952

over 20 minutes and urine is collected for the next 5 hours

Twelve normal subjects voided 1 200 1 900 cc during the five hour period In nine patients with Addison s disease treated with desoxycorticosterone and in two with untreated hypopituitarism the greatest five hour volume was 780 cc. *(Fig 110) Cortisone 50 mg orally four hours before ingestion* of water usually caused significant improvement sometimes *to normal ACTH therapy was effective in this manner only* in the patients with hypopituitarism Failure of water diuresis may also occur in hepatic and renal disease dehydration or edematous states

Effect of Salicylic Acid and Similar Compounds on Adrenal Pituitary System The extensive use of salicylic acid (SAL) in treatment of rheumatoid arthritis and rheumatic fever has led to the impression that this drug has some specific effect *in addition to its analgesic and antipyretic action* Georg Cronheim J Stanton King Jr and Nelta Hyder[8] (Bristol Tenn) studied the effect of SAL and related compounds on *the adrenal pituitary system by injecting the drugs subcu*taneously into normal and hypophysectomized rats and then measuring the amount of ascorbic acid in the adrenals Depletion of adrenal ascorbic acid indicates adrenal cortical activity Salicylic acid produced a significant depletion of adrenal ascorbic acid in the normal rats but had no effect in the hypophysectomized rats The depletion was in proportion to the amount of drug administered The lacl of effect in the hypophysectomized rats indicates the essential role of the pituitary and specifically ACTH in the mechanism of action of SAL This observation excludes any direct action *of SAL on the adrenals since removal of the pituitary* does not prevent the response of these glands to ACTH Salicylic acid therefore appears to have a specific direct or indirect action *on the anterior pituitary which results in production* or release of increased amounts of ACTH

A group of 12 aliphatic acids had no effect on the adrenal ascorbic acid content in normal rats A group of *20 aromatic* acids divided into substituted benzoic and substituted salicylic acid were injected into normal rats In the first group only two compounds benzoic and p methoxybenzoic acid produced a significant reduction in ascorbic acid Of 11 substi

(8) *Proc Soc Expe Biol & M d 80 51 55 May 1952*



Fig 111 —Typ l hyp t ph h g a d bo y tg owth ou d j ts (Co t y f K llg J H rt l Q rt J M d. 21 405 424 Octobe 1952)

pressure zones it leads to formation of peculiar ulcers with undermined edges Softening of the ligaments and other limb structures may cause the extremities to acquire a curious rubbery consistency The e changes give rise to pain and instability

Hyaluronidase metabolism was studied because of this noninflammatory alteration in the physical state of collagenized tissue Saline hyaluronidase wheals remained in the skin of the acromegalic patient for 52 21 (mean 10 5) minutes as compared with 07 50 (mean 2 2) minutes in a group of

is in itself without symptoms Considerable hypermetabolism may persist after inactivation of the acromegaly and then seems to exert no influence at all on the patients even in the long run

The dosage of the irradiation to the pituitary in acromegaly cannot be fixed at a standard level The best treatment is to administer three series of 3 000 r Additional irradiation is indicated in a few cases however the abatement of the acromegaly of soft parts requires considerable time so that the patients should presumably be observed for a couple of years before it can be decided whether the original treatment has been sufficient Defects of the field of vision constitute no indication for surgical intervention Only pronounced pressure symptoms with immediate risk of loss of vision may indicate operation

[My experience indicates too that surgery is rarely indicated in acromegaly if intensive roentgenotherapy is given early enough—Ed.]

Articular and Other Limb Changes in Acromegaly Clinical and Pathologic Study of 25 Cases is presented by J H Kellgren J Ball and G K Tutton[1] (Manchester Univ) Criteria for diagnosis were enlargement of the hands and feet together with coarsening of the features All patients had some clinical or radiologic evidence of a disturbance in the region of the pituitary fossa The series included 16 females and ages ranged from 13 to 67 The two youngest a boy 13 and a woman 24 were over 6 ft tall and might be considered giants Nine patients had never had significant pains in the limbs or back

There appear to be two clinical types of acromegalic arthropathy In one massive bony outgrowths and deformity of the bone ends lead to gross limitation of movement in many joints (Fig 111) The other more common condition is characterized by pains in the limbs and back with soft tissue enlargement of the joints excessive and abnormal mobility synovial thickening and recurrent effusions The characteristic radiologic finding is an increased joint space with remodeling of the bone ends This picture is unlike that of osteoarthritis or rheumatoid arthritis and is best described as acromegalic joint disease Macroscopic joint changes are shown in Figure 112 There may be hyperplasia and softening of the articular cartilage When this occurs in the deeper layers of the

(1) Quart J Med. 21 405-424 October 1952

pathologic states ferritin induced antidiuresis in dogs and rabbits was studied to establish the mechanisms through which it is mediated

Evidence was found that the antidiuretic effect of ferritin occurred through stimulation of the neurohypophysis to secrete an antidiuretic factor rather than by direct action of ferritin on the renal tubules Antidiuresis was induced by injection into the carotid artery of amounts of ferritin much smaller than required by the intravenous route Urine excreted during ferritin induced oliguria contained antidiuretic material of pitressin® like character as shown by its inactivation by thioglycollic acid Resection of the neurohypophyseal stalk with development of diabetes insipidus abolished the anti diuretic effect of ferritin in dogs which previously had been responsive

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DIABETES MELLITUS AND RELATED PHENOMENA

Analysis of Phenomenon of "Anticipation" in Diabetes Mellitus Arthur G Steinberg and Russell M Wilder[3] (Mayo Clinic) analyzed 200 family histories in which the ages of onset of diabetes in parent and child were reported examining the validity of the concept of anticipation as a physiologic phenomenon in diabetes The study shows that anticipation is a statistical and not a biologic phenomenon Accurate pre dictions based on the assumption that there is no physiologic relation between the ages of onset in parent and child were made of the frequency with which the age of onset would occur earlier in the child than in the parent and of the average difference in age of onset that would be observed in these cases

Unfavorable uterine environment provided the fetus by a diabetic or prediabetic mother is not a major factor in deter mining age of onset in diabetic offspring

The term anticipation should not be used in discussing observations relating to earlier age of onset of diabetes in the child than in the parent and the term prior onset should be used since it does not carry with it any of the physiologic implications of the term anticipation

(3) A n. I t Med 36 1285 1296 M y 1952

normal subjects This relative ineffectiveness of hyaluronidase in acromegalic skin might result from the presence of an excess of an antihyaluronidase but it seems more likely that it results from some alteration in the connective tissues them selves

Bilateral median nerve lesions were noted in three patients



Fg 112—S ct f n l kn l ft S ct on f k e h w g e la ged f m l c dyl th k d rt cul t l g d l gem t f l g m nts m s a d f ap t ll f t p d ght (C t y f K llg n J H t / Q a t J Med 21 405 424 O t be 1952)

and in one of these compression of the nerves in the carpal tunnel was relieved by decompression

[The occurrence of articular changes in acromegaly sometimes asso ciated with significant symptoms needs re emphasis —Ed]

Role of Neurohypophysis in Ferritin Induced Antidiuresis Silvio Baez Abraham Mazur and Ephraim Shorr[2] (Cornell Univ) state that the hepatic vasopressor principle ferritin (VDM) exerts a profound antidiuretic effect when given intravenously to hydrated dogs and rabbits Ferritin normally undetectable in the circulation is present in various experi mental and clinical conditions characterized by oliguria and edema formation including nutritional (low protein) cirrhosis in rats and decompensated hepatic cirrhosis the nephrotic syndrome and congestive heart failure in man To determine if ferritin was a factor in production of antidiuresis in these

(2) Am J Phys I 169 123 133 Ap l 1952

covered glycosuria should lead to a careful evaluation of the subject including testing of tolerance

[The two hour specimen in an oral glucose tolerance test is believed by many investigators to be the best test for diabetes —Ed.]

Effects of Stressful Life Situations on Concentration of Blood Glucose in Diabetic and Nondiabetic Humans Lawrence

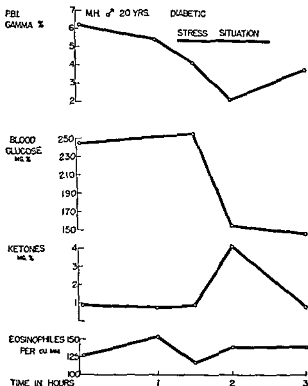


Fig 113 — R po to t t t d beti pat t (Court y f H kl L E J d W lf S D abet 1 383 39 S pt Oct. 1952)

E Hinkle Jr and Stewart Wolf (Cornell Univ) found that in nondiabetic and diabetic subjects the values for blood glucose circulating eosinophils serum phosphate and circulating protein bound iodine all fell during stress (Fig 113) The fall in glucose content was accompanied by a rise in ketonemia

(5) Diabet 1 383-392 Sept Oct. 1952

It is concluded (1) that prior onset of diabetes in the children of diabetic parents is frequently observed because (a) the age of onset of diabetes is highly variable and includes the reproductive period (b) nearly all diabetic patients who become parents become diabetic after age 30 and (c) there is no biologic relation between the age of onset in the parent and in the child and (2) the age of onset of diabetes in a parent cannot be used to predict the age of onset in the children

Glucose Tolerance III Evaluation of Four Types of Tests in a Heterogeneous Group of 71 Subjects with Glycosuria C Ray Womack (Vanderbilt Univ) and John H Moyer Jr[4] (Baylor Univ) performed three hour one dose oral (standard) and one hour two dose oral (Exton Rose) glucose tolerance tests in patients who have glycosuria without symptoms of diabetes Intravenous tests were made in 46 patients and post prandial sugar level was estimated in 62 instances two hours after a standard meal Fasting blood sugar levels per se were unreliable criteria for diagnosing diabetes or similar disturb ances of carbohydrate metabolism Although the intravenous tolerance test was less sensitive than the standard oral test both were considered satisfactory clinical tests for suspected diabetes The intravenous test eliminates changes resulting from variable gastrointestinal absorption but may overlook mild diabetes The standard test is simpler to perform and gives reliable information if gastrointestinal absorption is normal Postprandial blood sugar level can be measured simply and as a presumptive test for diabetes compares well with the standard test However the standard test applied to a two hour specimen only is equally simple and more satis factory The one hour two dose oral (Exton Rose) test should be discarded as too sensitive and unreliable

All tests should be repeated whenever normality or abnor mality are in doubt For proper evaluation the test results should be considered in the light of the patient s total problem

The correlation between degree of glycosuria and the severity of disturbance of glucose tolerance was poor Glyco suria is not diagnostic of diabetes As a result of renal mech anisms it may be detected in persons who show no evidence of disturbed carbohydrate metabolism However when dis

(4) Am. P a t 3 479 486 J 1952

may remain reasonably constant in dynamic balance because of continuous turnover of the population of glucose molecules as old molecules are replaced by new Diabetes an error of metabolism is characterized by hyperglycemia which may be a consequence either of excessively rapid absorption or synthesis or of impaired utilization of glucose Most investi gators agree that the chief primary metabolic defect is im paired utilization of glucose This impairment is apparently universal and includes the several normal fates of glucose i e glycogenesis fatty acid synthesis pyruvic and lactic acid formation and the total oxidation of glucose to carbon diox ide The author s study of the alloxan-diabetic rat has shown that the oxidation of glucose to carbon dioxide may fall below 50% of normal However in the rat made hyperglycemic by means of cortisone injection the rate of glucose production from noncarbohydrate precursors was six to seven times normal this may constitute a major contribution to the glycosuria

Insulin s precise locus of action is being pursued in various laboratories It is generally agreed that insulin s chief effect is on glucose utilization and that insulin must operate early in the sequence of events that initiates glucose utilization In sulin affects both glycogenesis and glycolysis Levine believes that insulin s function is to favor the entry of glucose into the intracellular compartment an action independent of phos phorylation Insulin s second possible locus of action is in the hexokinase catalyzed phosphorylation of glucose the neces sary initial chemical transformation that glucose undergoes when it enters the cell or immediately thereafter Cori *et al believe that insulin directly activates hexokinase by releasing* it from an inhibition due to anterior pituitary material Some question this explanation because it leaves unanswered the question of the extreme insulin sensitivity of the hypophysec *tomized animal Evidence for the antagonism between insulin* and the pituitary gland has repeatedly recurred in recent discussions of the problem

The impaired fatty acid and protein synthesis found in diabetes are not direct consequences of insulin lack but func tions of inhibited glycolysis encountered not only in diabetes but also in starvation There is no glycolysis to supply energy and reducing agents that are required in the synth

and diuresis Occasionally a diabetic subject had a rise in blood glucose content in response to stress situations of panic fear or intense rage probably due to elaboration of epinephrine and mobilization of liver glycogen Standard intravenous glucose tolerance tests performed in a setting of stress which evoked a reaction of anxiety and tension in the subject produced flatter curves than those seen during periods of relative relaxation and serenity Some patients however had higher glucose tolerance during stress situations of sadness resentment and loneliness

When glucose is given at a time of adaptation to stress situations it is apparent that two types of response may occur The glucose tolerance curve may be either flatter or more elevated than that seen in situations of relative serenity When a fasting person in a relatively serene state is exposed to a stressful situation the blood glucose content falls initially but as the exposure to stress continues he develops a ketonemic response and at this time the blood glucose level ceases to fall and may actually rise When a person in a relatively serene state is given glucose and at the same time is newly exposed to a stress situation the glucose tolerance curve is usually flatter than if he had not been exposed to stress If a person who has been exposed to stress for some time and has developed a ketonemic response is then given glucose the glucose tolerance curve is higher and more prolonged than it would be in the absence of stress Situations of acute stress are commonly associated with feelings of anxiety and apprehension whereas more prolonged stress situations are commonly associated with feelings of dejection loneliness and resentment This explains why the mood changes and changes of the glucose tolerance curve have a certain parallelism

In the labile diabetic who is exposed to rapidly changing life situations the occurrence of rapid changes in his capacity to utilize glucose appears to account for much of the difficulty in controlling the disease

[These studies help explain why emotional instability promotes lability in diabetic control —Ed]

Recent Contributions to Understanding of Experimental Diabetes DeWitt Stetten Jr[6] (Pub Health Res Inst of City of New York) states that the total glucose in the circulation

(6) J A M A 150 971 973 No 8 1952

nized for 18 years and who had had diabetes mellitus for 12 years He was maintained on a constant diet and unlimited fluids during the year of study Dosage levels were selected *to provide maximal glycosuria without ketonuria moderate* glycosuria aglycosuria with hyperglycemia and normoglycemia The level of adrenal function was estimated on the basis of serial eosinophil counts and measure of urinary corticosteroid values and urinary excretion rates of nitrogen sodium chloride and potassium

Large doses of insulin intended to insure continuous normoglycemia caused frequent insulin reactions and measurable increases in corticosteroid excretion rates Small doses which just sufficed to prevent ketonuria had no detectable effect on the rate of corticosteroid excretion or the eosinophil count although a heavy glycosuria ensued Possible secretion of an adrenocortical salt hormone during this regimen is suggested by the gradual conservation of sodium and chloride despite continuing glycosuria

Urine volumes were greatest in the intervals of attempted normoglycemia when they even exceeded volumes in periods of maximal glycosuria Sodium and chloride excretion rates except during initial maximal glycosuria did not significantly alter Potassium and nitrogen excretion rates varied inversely with amounts of insulin administered

[It is clear from these studies as well as from those of Somogyi and others that insulin hypoglycemia stimulates increased adrenocortical function thereby antagonizing the action of insulin. These phenomena account for many instances of brittle diabetes

In another study (J Clin Endocrinol 10 307 March 1950) McArthur found in diabetic acidosis an increase in the urinary excretion of corticoids when diabetes is satisfactorily controlled there is a subnormal excretion With stressful phenomena according to Wolfe and Paschkis (Metabol m 1 413 1952) the adrenal response of the diabetic tends to be subnormal —Ed]

Effect of Cobaltous Chloride on Blood Sugar and Alpha Cells in Pancreatic Islets of Rabbit. Martin G Goldner Bruno W Volk and Sidney S Lazarus[9] (Jewish Sanitarium and Hosp for Chronic Diseases Brooklyn) injected 25–40 mg/100 cc of cobaltous chloride as 0 5% solution in saline intravenously into 16 female rabbits The animals were killed one hour to four days after the injection Blood sugar content was determined before and at various intervals after the injection

(9) Metabol m 1 544 548 N mbe 1952

Response of Liver to Insulin in Normal Subjects and in Diabetes Mellitus Hepatic Vein Catheterization Studies. A G Bearn Barbara H Billing and Sheila Sherlock[7] (Post graduate Med School London) catheterized the hepatic vein in 35 diabetic patients and 15 normal controls to study the effect of insulin on the liver With 0 1 unit of insulin/kg intravenously the output of hepatic glucose in both normal and diabetic subjects dropped immediately When normal subjects became hypoglycemic the output of hepatic glucose the flow of hepatic blood the concentration of venous lactic acid and the consumption of splanchnic oxygen increase The release of adrenaline may have been responsible for these events which did not take place in the diabetic patients who of necessity did not become hypoglycemic The output of hepatic glucose is depressed after insulin for a longer time in the diabetic than in the normal subject

In the normal subject the restoration of blood glucose concentration to normal after insulin is not due to adrenaline alone The liver may possess an inherent homeostatic property of maintaining a normal blood glucose level The alpha cell hormone obtained from the pancreatic islets is glycemic and acts directly on the liver

In diabetic ketosis the concentration of ketones is greater in the hepatic venous than in the peripheral venous blood The difference is greatest in patients with the greatest ketosis Insulin does not appreciably diminish the blood ketone values Diabetic patients have a higher fasting splanchnic oxygen consumption than normal subjects This can in part be related to hepatic ketone production

The depression of hepatic splanchnic oxygen consumption and the increased peripheral utilization of glucose after insulin both play a part in lowering capillary glucose concentration

Metabolic Study of Diabetic Patient Effect of Variations in Dosage of Insulin on Adrenal Cortical Activity and on Water, Electrolyte and Nitrogen Excretion J W McArthur, D H C Chao E A MacLachlan M F Morrill A M Campbell M D Wood A. Zygmuntowicz F C Goetz and S L Sveinsson[8] (Harvard Med School) used crystalline insulin in doses ranging from 25 to 80 units for 15 day periods Their subject was a youth 19 in whom mongolism had been recog

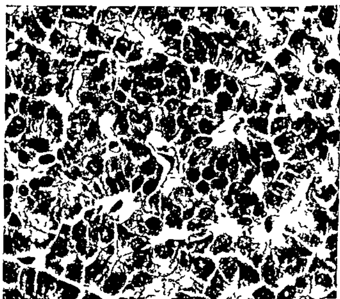
(7) Clin Sc. 11 151 165 May 1952
(8) J Clin Invest 31 592 597 June 1952

Zinc Insulin Preparations for Single Daily Injection Clinical Studies of New Preparations with Prolonged Action. K Hallas Møller M Jersild K Petersen and J Schlichtkrull[1] (Copenhagen) made three preparations of the zinc insulin type with activity ranges from about 18 hours to over 30 hours and tested them clinically in 65 patients with severe cases of diabetes The results showed that satisfactory blood sugar control can be obtained in these patients with a single daily injection of the appropriate one of the three types The three types were (1) a suspension of amorphous precipitated insulin containing 2 mg zinc/1 000 units of insulin with a pH of 7 2 and an average activity range of about 18 hours (2) a suspension of ground insulin crystals (particle size about 0 002 mm) containing 2 mg zinc/1 000 units with a pH of 7.2 and an average activity range of about 24 hours and (3) a suspension of insulin crystals (particle size 0 01-0 02 mm) containing 2 mg zinc/1 000 units with a pH of 7 2 and an average activity range of about 30 hours

These three types of insulin fast medium and slow acting have considerably simplified the troublesome adjust ment of difficult cases By determining the patient s reaction type (A B or C) the preparation that gives the most satis factory adjustment can be chosen The A B and C reactions designate in a simple way the different sugar curves obtained the patient with an A reaction reacts quickly to a preparation but the effect is insufficient during the night with a B reac tion the insulin supply is adequate for 24 hours with a C reac tion the patient reacts too slowly to insulin to obtain sufficient effect during the daytime The aim of insulin therapy is to obtain with a single daily administration the B reaction in all diabetics A fast reacting patient needs a slow acting insulin in order to have the B reaction whereas a slow reactor requires a fast acting preparation The most suitable insulin prepara tion or combination of preparations must be carefully selected Preparations of the zinc insulin type can be made with con siderably varied ranges of activity The preparations are mutually miscible It is possible that only types of zinc insulin preparations may be necessary because of the miscibility of such preparations

(1) J A M A 150 1667 1671 Dec 27 195

Twenty four hours after the injection of cobalt complete absence of alpha cells from many of the pancreatic islets was noted Other islets contained some alpha cells (Fig 114) which were considerably disintegrated as evidenced by degranulation loss of nuclei and haziness of the cellular outline Very few normal islets remained The beta cells and the exocrin portion of the pancreas appeared intact After 48 hours there



F g 114 —P nc t let of bb t k ll d 24 h aft r nt ou je t f 40 mg f 0 5% sol t o f balt hl d Alpha ll mpl tely ab t B ta c ll nd xoc po t f panc nt t G m ta d ed f om ×500 (Co rt y of G ld r M G t l Met bol m 1 544 548 No emb 1952)

was further alpha cell damage and fewer remaining normal islets

The blood sugar level rose significantly soon after the injection and returned to the normal range within four to five hours A second intravenous injection of cobalt repeated after 48 hours was followed by a second rise of the blood sugar level No hypoglycemic levels were encountered after the administration of cobaltous chloride

Cobaltous chloride is a valuable tool for the study of the pancreas and diabetes mellitus

Zinc Insulin Preparations for Single Daily Injection *Clinical Studies of New Preparations with Prolonged Action* K Hallas Møller M Jersild K Petersen and J Schlichtkrull[1] (Copenhagen) made three preparations of the zinc insulin type with activity ranges from about 18 hours to over 30 hours and tested them clinically in 65 patients with severe cases of diabetes The results showed that satisfactory blood sugar control can be obtained in these patients with a single daily injection of the appropriate one of the three types The three types were (1) a suspension of amorphous precipitated insulin containing 2 mg zinc/1 000 units of insulin with a pH of 7 2 and an average activity range of about 18 hours (2) a suspension of ground insulin crystals (particle size about 0 002 mm) containing 2 mg zinc/1 000 units with a pH of 7.2 and an average activity range of about 24 hours and (3) a suspension of insulin crystals (particle size 0 01-0 02 mm) containing 2 mg zinc/1 000 units with a pH of 7 2 and an average activity range of about 30 hours

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(1) J A M A 150 1667 1671 Dec 27 1952

Denatured Insulin Simplified, Rapid Means of Treatment of Allergy to Insulin Complicating Diabetic Ketosis is described by Henry Dolger (*Mount Sinai Hosp New York City*) Sensitization to insulin develops gradually so that generalized symptoms appear only after the first or second week of treatment or immediately after reintroduction of therapy after a lapse of several months or years Sensitization usually assumes the nonspecific picture of general urticaria dyspnea stridor and arthralgias Allergy to insulin can seriously interfere with the therapy of diabetes mellitus These generalized allergic reactions do not respond satisfactorily to antihistamines In an acute insulin emergency either rapid desensitization which requires 24-48 hours to become effective or use of denatured insulin is indicated The latter is preferable to rapid desensitization because it is simple and quick

Insulin can be denatured by boiling Regular and crystalline zinc insulin being in an acid medium can withstand boiling for three hours and retain half their physiologic activity Boiling for 15 minutes results in loss of only 10 20% of insulin activity Only the clear rapidly acting unmodified insulins regular and crystalline zinc can be used for denaturing by heat a process not applicable to the modified types protamine zinc, globin and NPH insulin Once desensitization has been accomplished in the patient with generalized allergic reactions in about two to three weeks any type of commercially available insulin may be used without difficulty Four patients with constitutional allergic reactions and six with fairly severe local cutaneous reactions have been treated by denatured insulin with uniform success

Man 49 with diabetes mellitu had taken insulin intermittently for six years for brief periods Ten days after the first administration generalized urticaria dyspnea and malaise developed requiring epinephrine for relief Insulin was discontinued and at various times attempts to reinstate therapy evoked the same generalized allergic pattern regardless of the type of insulin used or antihistamine therapy When seen in May 1949 he presented the classic symptoms of diabetes with acidosis and a blood sugar level of 428 mg/100 cc Subcutaneous administration of crystalline zinc insulin resulted in another allergic attack which required epinephrine A vial of crystalline zinc insulin (U80) was boiled for 30 minutes and 10 units was injected subcutaneously four hours after the allergic reaction had subsided No allergic manifestations appeared Admin

(2) N York J Med 52 023 024 A g 15 195

istration of the denatured insulin was repeated in an hour and every two hours thereafter until a total of 60 units had been given and the patient was no longer acidotic He was kept on 20 units of denatured insulin twice daily for one month then transferred to 40 units of globin insulin daily The transfer was effected unevent fully and the patient has been free from any disturbance due to daily insulin administration

√ [This is an interesting observation as is that of De Filippis nd Ian naccone (Lancet 1 119 1193 June 14 195?) who found that the gamma gl bul n of the serum of a patient with insulin resistance pos essed marked in ulin neutrali ing activity —Ed]

Skin Necroses Due to Insulin in a Diabetic H Bartelheimer[3] (*Univ of Kiel Germany*) reports a case

Man 27 with known diabetes for 10 year had numerous de



Fig 115 — Symm t l l l t pp th gh f sk n d t (C t y f B t lh m H S h med. W h h 82 573 574 M y 3 195)

pressions at insulin injection sites on the thigh They were sharply demarcated funnel shaped and had a thin wrinkled base (Fig 115) Three months after discovery of the diabetes and use of insulin indolent indurations had occurred at injection sites and 10 days later wedge shaped pieces of skin were ca t off Healing of the defect was often low and sometimes necrotic tis ue had to be removed Inflammatory reaction was ab ent Injections were continued on the thigh Injection on the lower leg or upper arm caused no reaction The skin defects rapidly assumed the present appearance New

(3) Schw med W h sch 8 573 574 M y 23 1952

depressions formed for about two years but none after that time The diabetes was always well controlled Polyneuritis and circulatory disturbances were absent

The condition is not an insulin dermatitis due to impurities in the insulin and the appearance of necrobiosis lipoidica is quite different Localization and manifestations indicate an atypical variant of lipodystrophy

Modern Treatment of Diabetes Mellitus Henry T Ricketts[4] (Univ of Chicago) stresses four principal objectives in diabetes therapy relief of symptoms maintenance of normal nutrition preservation of the insulin producing capacity of the pancreas and prevention of or minimizing complications The first two objectives are not difficult to attain Prevention of hyperglycemia can preserve the pancreas and help to prevent complications Preliminary treatment of uncomplicated diabetes in the ambulatory patient involves reduction of glycosuria and assessment of the severity of the disease and the need for insulin

The diet should contain 100 150 Gm of carbohydrates equally apportioned among the three meals 1 Gm or more of protein/kg body weight and enough fat to complete the caloric requirement The patient should know how to test his urine qualitatively for sugar four times a day and should be given a diabetic manual to read He should be seen at weekly or biweekly intervals for urine tests re evaluation of diet and a quantitative test for sugar on a 24 hour urine sample If the patient is obese the low carbohydrate diet is continued even if home tests show no sugar If his weight is normal carbohydrates can be cautiously added to the diet If there is weight loss carbohydrates and calories are increased and if glycosuria results insulin is added If the patient is obese and home tests show considerable sugar the diet is continued until weight diminishes This will often clear up the glycosuria If not insulin is added If the patient loses sugar and has a normal weight the carbohydrate content of the diet is increased and insulin added If a diet that is designed to correct abnormal or maintain normal body weight fails to free the urine of sugar within two to four weeks insulin therapy is indicated

The first consideration in the maintenance period is the caloric value of the diet Basal requirement is 20 25 calories/

(4) J A M A 150 959 961 Nov 8 1952

kg standard weight with a 20 30% increment for activity for the sedentary 30 50% for the moderately active and 50-100% for the strenuously active patient About 1 Gm protein/kg body weight should be included its caloric value is then sub tracted from the total and the remaining calories are equally divided between carbohydrates and fat

The ideal preparation is NPH insulin best begun with a 10-20 unit daily dose one half hour before breakfast The carbohydrate distribution among the various meals should allow more for lunch than for breakfast or supper and a small bedtime feeding besides Insulin dosage is increased by 3 5 units every three to five days until the urine specimen on rising or in the afternoon is sugar free or nearly so If glyco suria persists after breakfast 5 10 units of crystalline insulin is mixed with the NPH preparation taken before breakfast If glycosuria persists after supper a small dose of crystalline insulin before that meal may be necessary A short acting insulin should never be given at bedtime when a long acting preparation is being used

Blood sugar level measured two or three hours after a meal is most informative such analyses have to be made once a week at an early stage then once a month to once in three months in the average case

Insulin requirements in the brittle diabetic should be so adjusted that the lowest levels of blood glucose never fall below 100 120 mg/100 cc Glycosuria will be excessive some of the time Control is smoothly maintained with crystalline insulin given two or three times a day before meals with perhaps a minimal dose of protamine zinc insulin before breakfast

Diabetic Coma—Therapeutic Problem Garfield G Duncan[5] (Pennsylvania Hosp Philadelphia) calls attention to the importance of early diagnosis of diabetic coma Such a diagnosis is possible in the home by simply finding grade 4 reactions for glycosuria and ketonemia by qualitative tests in a subject with clinical evidences of ketosis Initial therapy with insulin fluids and sodium chloride should be started at once Regular insulin 100 units and 8 oz of a salty broth should be given The patient should then be brought to the hospital where blood sugar level CO_2 combining power hematocrit

(5) Ann I t M d. 37 1188-1196 D cembe 1952

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The first consideration in the maintenance period is the caloric value of the diet Basal requirement is 20-25 calories/

(4) J A.M A. 150 959 961 Nov 8 1952

hours of therapy Intravenous administration of fluids is discontinued as soon as the patient can take adequate fluids orally Hypopotassemia can be detected quite early by the ECG and the clinical danger of hypopotassemia is postponed several hours After six hours of therapy potassium can be given orally or intravenously if renal function is good and urine output is adequate Patients in profound ketonemia can be given a solution of multiple electrolyte composition intravenously Glucose solutions are not necessary parenterally while extreme degrees of hyperglycemia persist Glucose can be given parenterally when the blood sugar is below 300 mg/100 cc It will protect against the danger of a rapidly developing hypoglycemia in patients who become sensitive to insulin rapidly at a time when their glycogen stores are depleted it alleviates tissue starvation and is important in reducing excessive ketone production

The disappearance of excessive ketoacids and the release of base that accompany therapy make the routine use of alkali unnecessary But if the degree of ketosis is extreme and the patient is greatly hyperpneic sodium R lactate in an amount calculated to raise the CO combining power 10 15 vol % and no more can be used

Diabetic Acidosis as defined by John P Peters[6] (Yale Univ) is the natural consequence of the inability of an animal that is conditioned to subsist on a carbohydrate diet to oxidize carbohydrate Ketosis is an adaption to deficient carbohydrate combustion About two thirds of the carbohydrate expended by a normal person is converted to fat and then burned Conversion of carbohydrate to fat requires the expenditure of a certain amount of energy and cannot be effected if there is no carbohydrate or if carbohydrate cannot be oxidized In the intermediary metabolism of food the products of both fat and carbohydrates are oxidized in the same burner the Krebs cycle but the 2 carbon groups usually offered to this burner from fat cannot be used for the renewal of the primary element of the burner the 4 carbon group oxalo acetic acid This requires products of carbohydrate If this is not provided protein is broken down At the same time the liver is activated to couple 2 carbon groups from fat into the 4 carbon groups acetoacetic acid and β hydroxybutyric acid

(6) M t lxl m 1 2 3 235 May 1952

blood specific gravity and urea nitrogen level are determined The urine is tested for sugar acetone culture and sediment an ECG is made and blood pressure is recorded For clinical purposes glycosuria and a 4 plus reaction for acetone in the plasma are the criteria for diagnosis The qualitative tests for hyperketonemia on undiluted plasma and on various dilutions give more reliable indications of the gravity of the ketosis and the prospective need for insulin than does a knowledge of the CO_2 combining power or sugar content of the serum The CO_2 combining power may give false information in the presence of renal failure or hypoventilation

At Pennsylvania Hospital when a grade 4 reaction for plasma ketones is found a sample of plasma is diluted 1 1 with normal saline if this dilution still gives a grade 4 reaction for acetone ketonemia is of severe degree and large amounts of insulin will be tolerated at the beginning of therapy This diluted mixture is further diluted 1 1 with normal saline and if a grade 4 reaction is still elicited ketosis is of a profound degree In such cases the apparent effectiveness of insulin is greatly impaired and as much as 300 units of regular insulin is given as the initial dose If the patient has a grade 4 reaction for acetone in the undiluted plasma but only grade 3 or 2 on the first dilution he is more sensitive to insulin and 100 units of regular insulin is given 40 units intravenously and 60 units subcutaneously with 25 units at one hour intervals until the undiluted plasma gives less than a grade 4 reaction Thus 100 units of regular insulin is given as the initial dose if the grade 4 reaction for plasma acetone is obtained only in the undiluted plasma 200 units if it is also obtained in the first dilution 300 units if it is observed in the second dilution and 400 if it occurs in the third dilution A decrease in the ketone content of the plasma is detectable before any apparent reduction in ketonuria When this occurs there is a rapid return of sensitivity to insulin and the amount is reduced and only given every four to six hours If there is no reaction with the qualitative tests for ketonemia and glycosuria subsides glucose is administered and insulin therapy withheld until glycosuria returns

Adults in diabetic coma are given fluids intravenously until the blood pressure and hematocrit are normal No attempt is made to correct deficits of electrolytes during the first few

creased to 20 Gm /hr The glucose and saline should be given separately Nothing should be given by mouth until the patient is conscious and free from nausea and vomiting Blood should be ready for transfusion in case the patient goes into shock Potassium and phosphate are lost from the cells during acidosis and should be replaced during treatment to prevent depletion The serum potassium level is the best guide to the administration of potassium The frequency and danger of heart failure due to potassium loss has been exaggerated

[The reader is referred to the original article for careful study of Peters discussion of diabetic acidosis and to the work of Gue t *et al* (Diabetes 1 276 1952) which indicated that acidosis produced by administration of ammonium chloride intensified the diabetic status of alloxanized rats —Ed]

Electrolyte Metabolism in Diabetic Acidosis Randall G Sprague and Marschelle H Power[7] (Mayo Clinic) review changes in the blood serum that can be estimated easily in most laboratories and provide guidance for therapy in diabetic acidosis Excessive loss of potassium the principal intracellular cation from the cells during acidosis probably represents withdrawal of potassium with water during the process of abnormal cellular metabolism and dehydration Some potassium is also lost by emesis Despite the accelerated excretion of potassium during acidosis the ion tends to accumulate in the serum and the concentration may be normal or slightly elevated before institution of treatment (Fig 116) Urinary excretion is unable to keep pace with the rapid discharge of potassium from the cells into a volume of extracellular fluid that is progressively diminishing After a few hours of treatment with fluids the serum potassium concentration has been reduced by dilution and urine excretion Considerable amounts of potassium may be removed from the extracellular fluid owing to deposition with glucose or protein The clinically important symptoms associated with hypopotassemia are due to impaired function of skeletal muscle and myocardium These include muscular weakness and heart failure Respiration may be decreased because of muscle weakness leading to hypoventilation and maintenance of low CO_2 tension in the extracellular fluid The ECG reveals prolongation of the Q T interval and broadening and flattening of the T wave

It is not necessary or safe to administer potassium in the early hours of treatment when concentration in the serum is

(7) J.A.M.A. 151 970 976 M 21 1953

In the absence of insulin the block is exaggerated Blood sugar rises destruction of protein increases and the production of ketone bodies is accelerated One of the actions of insulin is the facilitation of the formation of fat from carbohydrate The ketone bodies produced from fat are not as efficient as carbo hydrate products in maintaining the integrity of the Krebs burner

The diabetic subject is more sensitive than the normal person to the effects of starvation and carbohydrate deple tion Diabetic ketosis and acidosis are not attributed to over indulgence in carbohydrate food per se Ketosis and acidosis naturally follow prolonged periods of hypoglycemia from insulin The hyperglycemia and glycosuria in acidosis results in dehydration of the cells and decrease in the serum concen tration of salt The serum drop in sodium and chloride con centration is due to the dilution of the serum with intracellu lar fluid loss Hyperglycemia induces absolute depletion of sodium and chloride in the body however as long as hyper glycemia persists the magnitude of this depletion is not so great as the depressed concentrations of sodium and chloride in the serum indicate The extreme diuretic effect of the glu cose causes dehydration The dehydration and salt loss are the major cause of shock and coma in diabetic acidosis Bi carbonate is also reduced The difference between sodium and chloride is a more useful measure of bicarbonate than is bi carbonate itself The major portion of the reduction of bi carbonate is the product merely of replacement of this anion by ketone acids The use of bicarbonate or lactic acid is not necessary in the treatment of acidosis

From the standpoint of carbohydrate metabolism fat me tabolism ketosis and destruction of protein the first consider ation of treatment is to restore as rapidly as possible the ability to oxidize carbohydrate Generous amounts of insulin are needed Frequent moderate doses of insulin 50 units or less must be given with the blood sugar content serving as the most important guide The administration of glucose facili tates the combustion of carbohydrate Glucose must be given in moderation Water and saline must be given A 5% solution of glucose together with saline solution should be given at the onset of treatment and the glucose infusion should be continued at the rate of about 10 Gm /hr until the blood sugar takes a decided downward trend then the rate is in

from the cells are lost by urinary excretion The concentration of phosphorus is usually high early in the course of treatment and then diminished The effects of hypophosphatemia are not known

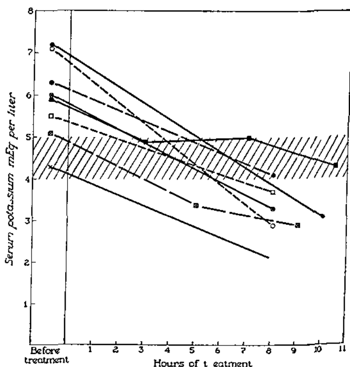
Chloride and sodium are lost in the urine in large quantities during development of diabetic acidosis The chloride deficit may not be evident from the serum chloride level which may be normal or elevated Loss of sodium chloride leads to dehydration vascular collapse renal insufficiency and coma and replacement is imperative Excess amounts of chloride must not be given because the serum bicarbonate will be displaced by chloride as well as by ketone acids and other anions delaying correction of acidosis Acidosis due to excessive amount of chloride may replace the ketone acidosis The rate of administration of chloride should not exceed the ability of the kidneys to dispose of excess amounts The chloride in the replacement fluid should not exceed its normal concentration in the extracellular fluid which is about 100 mEq /L

The fluid loss in acidosis may be considerable and fluids should be replaced quickly intravenously The first 1 2 L should be given rapidly and the rest of the fluid during the first 12 24 hours Fluids can be given orally as soon as the patient can take them Fluids for formation of urine can be given later Whole blood or plasma may be needed if the patient is in shock

There is a difference of opinion concerning the value of early administration of glucose in the treatment of acidosis Theoretically if enough glucose is given to maintain hyperglycemia and extracellular hypertonicity it may be harmful by preventing the cells from recovering lost water On the other hand if glucose is not given in quantity sufficient to maintain the blood sugar at a high level much of the theoretical advantage of its administration (i e acceleration of glucose utilization) is lost Later in treatment when a supply of electrolyte free water may be desirable to promote formation of urine solutions of glucose can and must be used if oral intake is not possible

Accurate replacement of losses of water and electrolytes cannot be expected to prevent some fatalities among patients who *are in irreversible shock or who have serious complicating illnesses*

elevated or normal It should be given about four hours after therapy begins Using the flame photometer determination of the serum potassium level as a guide about 20 25 mEq potassium/hour should be given to a total of about 100 mEq Since deficiency of potassium is associated with deficiency of phosphorus both can be given in the form of a buffered solution



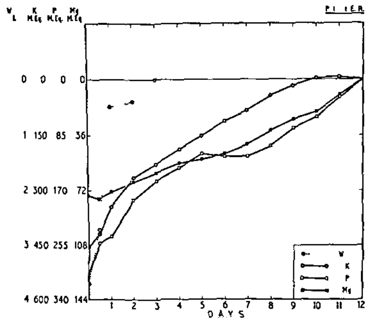
F g 116—Ch ng n pot m t t n n xt ll l fl d as m d n blood m d g t tment of d b t d s n e ght p t nt N m l ge is nd cated by h d d rea (C tesy of Sp ag R G d Power M H J A M A 151 970 976 M 21 1953)

of potassium phosphate A 5 cc ampule of aqueous solution containing 2 Gm dibasic potassium phosphate and 0 4 Gm monobasic potassium phosphate provides 25 89 mEq potassium and a mixture of monohydrogen and dihydrogen phosphate (14 4 mM phosphate) The contents of 1 ampule are added to whatever fluid is being administered intravenously

The behavior of potassium in diabetic acidosis is paralleled by that of phosphorus Large quantities of phosphorus mostly

of nitrogen The third stage of recovery begins when a positive balance of cell nitrogen is achieved about the seventh day of treatment This stage is associated with the retention of additional amounts of intracellular electrolytes and is not completed by the end of 10 12 days

The mean restoration of cell electrolytes for 1 73 sq m of body surface was 339 mEq potassium 40 mEq magnesium



F g 117 —C ll l r t r t d g ry f m d b t d C m l ti ell b l f w t d l t lyt t d f h g n ll t g O d nat l p p t t mal c t t f p ta m m gn s m and l b l h ph ru ll w t (C t y f Nab J D N t l Q t J M d 21 2 5 248 Ap l 1952)

and 66 mEq phosphorus Calculated in terms of total cell constituents the retention of phosphorus was relatively less than that of potassium When the retained phosphorus was all considered as cell labile organic phosphate the recovery was seen to be proportional The rapid uptake by the cells of potassium magnesium and phosphorus without a corresponding positive nitrogen balance may be related to a restoration of depleted cell glycogen and organic phosphate A secondary

Metabolic Studies in Severe Diabetic Ketosis *J D N Nabarro A G Spencer and J M Stowers*[8] *(London)* performed metabolic balance studies of 19 diabetic patients during recovery from ketosis Treatment was guided by frequent estimations of the blood sugar level plasma electrolytes and bicarbonate reserve In the first 24 hours 100 500 units of insulin were given by intravenous and intramuscular injection Rehydration was begun with 1 5 3 L normal saline or lactate saline solution without glucose given intravenously over three to six hours As soon as the blood sugar and plasma potassium levels began to fall this was replaced by a 5% glucose solution containing sodium potassium chloride lactate and phosphate 2-4 L being given over 12 24 hours Oral feeding was then begun

The study showed that whereas the restoration of the depleted extracellular fluid is rapid with appropriate treatment cellular recovery is slow and may indeed take several weeks to complete The cell constituents may be restored at widely different rates and not necessarily in the proportions found in normal cells

During recovery from ketosis the mean restoration of water and electrolytes in the extracellular fluid for 1 73 sq m of body surface was 2 9 L water 428 mEq sodium and 390 mEq chloride This is equal to 20 25% of the normal total volume of extracellular fluid Restoration of the extracellular fluid was rapid and largely complete in less than 48 hours In the early period of treatment there was a continuing excessive loss of water sodium and chloride in the urine and the extent of these losses was closely related to the degree of glycosuria Since glycosuria is inevitable in the initial stages of treatment the amounts of water and electrolytes that need to be given to restore the extracellular fluid are always greater than the quantities which are retained

Cell recovery occurs in three main overlapping phases (Fig 117) In the first water without an equivalent amount of electrolytes is rapidly taken up by the cells as the blood sugar falls This is a physical response to differential changes in osmolarity between the extracellular and cell fluids In the second stage lasting 6-10 days potassium magnesium and phosphate ions are restored to the cells together with additional quantities of water but without an equivalent amount

(8) Q J Med 21 225 48 April 1952

sodium carbonate A small amount of powder is deposited on a piece of nonabsorbent white paper and sufficient plasma or serum added (2 3 drops) to saturate the powder At three minutes the test correlates well with CO content of the plasma A deep purple color is a 4 + reaction and a trace to 3 + reactions are represented by degrees of lavender and purple Gross hyperlipemia interferes with the rate of the reaction and the depth of color changes

When a 4 + serum acetone reaction is found in a patient who has not received treatment for diabetic acidosis the CO content is usually 10 mEq/L or less A 4 + reaction is consistent with a minimum of about 40 mg of total ketone bodies in 100 cc whole blood A 2 + or 3 + reaction is usually accompanied by CO_2 values between 10 and 20 mEq/L A trace or a 1 + reaction seems to be accompanied by CO_2 values in the normal range or only slightly depressed

In 25 patients studied with concurrent CO determinations 4 + reactions for urinary sugar and acetone and a 4 + reaction for serum acetone were consistent with the diagnosis of chemical coma Patients with a 4 + serum acetone content determined by the nitroprusside method need insulin usually 100 units of regular insulin is necessary The blood sugar value must be determined 2½ 3 hours after the first dose of insulin and more insulin given if necessary Carbohydrate can be given orally or intravenously Patients with a 2 + or 3 + serum acetone reaction are not so critically ill but must be watched carefully

The nitroprusside test can differentiate diabetic acidosis from diabetic nephropathy with renal acidosis posthypoglycemic states and nausea vomiting and abdominal pain due to benign or serious intra abdominal conditions

Importance of Control of Diabetes in Prevention of Vascular Complications Nils R Keiding Howard F Root and Alexander Marble[1] (Boston) studied the incidence and extent of retinopathy arterial calcification and nephropathy in 451 patients who became diabetic before age 30 and had had the disease for 10-36 years The data were correlated with sex age of onset insulin dosage duration of diabetes and degree of control Apparently sex was not a significant factor neither was age at onset except that patients who became diabetic between ages 10 and 19 9 years apparently had the highest incidence of nephropathy Patients who took less than 30

(1) J A M A 150 964-969 N 8 1952

factor is the change in base binding power of cell protein with the correction of acidosis The restoration of cell electrolytes is hastened by the administration of potassium and phosphate ions During the early stages of treatment large transfers of sodium ion into the cell occurred This can be reduced by adequate supplements of potassium The delay in achieving a positive cell protein balance has been correlated with two main factors (1) the comparatively low protein intake in the early stages of treatment and (2) the catabolic response associated with overactivity of the adrenal cortex as measured by the increased urinary excretion of 11 oxysteroids

Before treatment the plasma levels of potassium magnesium and phosphorus were normal or high despite cell depletion of these electrolyte The rapid catabolism of uncontrolled diabetic acidosis causes these ions to move out of the cells into the extracellular fluid and plasma faster than they can be excreted by the kidneys whose function is impaired by dehydration Within a few hours after start of treatment the plasma levels of potassium magnesium and phosphorus all fall below normal levels This fall results from the movements of these electrolytes back into the cells and also from urinary losses as renal function returns with the correction of dehydration Renal conservation of magnesium and phosphorus is soon highly effective and they almost disappear from the urine Potassium is not so well conserved and continues to be lost in the urine despite low plasma potassium levels and cell depletion Serious hypokalemia was prevented by early intravenous administration of potassium and none of the patients had any of the symptoms and signs which have been described in association with very low plasma potassium levels

[These studies re emphasize the enormous restitution of various chemical components that is necessitated after diabetic acidosis several days are required to reach normal equilibrium —I d]

Clinical Application of Simple Qualitative Serum Acetone Test in Diabetes Mellitus Otto C Page[9] (Univ of Oregon) describes a simple nitroprusside qualitative test for serum or plasma acetone which may yield additional information of aid in evaluation and treatment of the acutely ill diabetic patient

METHOD —Nitroprusside powder obtainable commercially or easily prepared in any laboratory is composed of 1 Gm finely ground sodium and 60 Gm each of ammonium sulfate and anhydrous

(9) New England J Med 248 95 97 Feb 12 1953

Degenerative Vascular Complications in Juvenile Diabetes Mellitus Treated with "Free Diet" Y Larsson A Lichtenstein and K G Ploman[2] (Stockholm) made a follow up examination of 257 patients with diabetes mellitus beginning in childhood All had been treated with controlled insulin therapy and were permitted a normal diet corresponding completely with that of healthy children Glycosuria was permitted but did not exceed 10 20 Gm/24 hours The fasting blood sugar level was kept below 200 mg/100 cc Most patients were between 10 and 20 at onset of the disease 66 were followed for less than 5 years 75 for 5 10 years 62 for 10 15 years and 44 for more than 15 years

Mortality rate was 6 9% Incidence of all types of diabetic retinopathy was 33 2% Frequency of retinopathy was correlated to the duration of the disease After more than 15 years duration of diabetes 12 1% had reached the stage of proliferative retinitis Incidence of albuminuria as an indicator of diabetic nephropathy was 15 6% After more than 15 years of diabetes 30 3% had albuminuria Incidence of vascular calcifications in the legs after 15 years of diabetes was 14 3%

Results were compared with those of other authors using measured diets In general the frequency of vascular lesions was the same in the present group as in diet treated patients except for vascular calcifications which were less frequent than in most other series

It is concluded that the use of measured diets does not protect diabetic children against degenerative vascular complications to a greater extent than treatment with a free and normal diet which is combined with adequate insulin therapy and regular and continuous control This form of treatment is consequently considered preferable because of its obvious advantages in offering the diabetic children a chance for a more natural and normal life Etiologic factors responsible for the degenerative vascular complications are unknown

Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis Preliminary Observations of Effect of Heparin on the Disease H Engelberg J Gofman and H Jones[3] (Univ of California) determined the values of the serum cholesterol phospholipids total lipids and the S_f 12 20 20 35 and 35 100

(2) D betes 1 449 458 N v De 1952
(3) Ib d pp 425-433

units of insulin a day had complications as often as the group as a whole

Control of diabetes materially lowered the incidence of complications but the decrease was not influenced by variations in duration of the disease age at onset or insulin dose The degree of control was excellent under the following conditions (1) if the patient had never been in coma (2) if insulin therapy had been begun within a few weeks of onset of diabetes (3) if the urine was tested for sugar oftener than once daily from the time of onset with a conscientious attempt to free or nearly free the urine of sugar before meals by adjusting insulin dosages on the basis of the results of urine tests (4) if the patient s food was weighed at least 80% of the time from the onset of symptoms (5) if physical examinations and laboratory tests were faithfully carried out at least once a year by a physician and blood and urine test results were satisfactory

Of 32 patients with excellent or good control maintained for 20 years or longer none had grade 4 retinopathy and only 1 had grade 3 changes Among 157 patients who were diabetic as long but had only fair or poor control 16% had grade 4 and 15% had grade 3 retinopathy With excellent control no patient had more than minimal retinopathy (grade 0 or 1) Among 189 patients who had been diabetic for 20 years or longer 60% of 32 with excellent or good control had only minimal changes or no arterial calcification whereas only 20% of 157 patients with fair or poor control escaped with such slight arteriosclerosis Of the entire series 22% had diabetic nephropathy a complication seen in none of the 11 patients with excellent control in only 1 of the 50 under good control but in 17% of the 92 with fair and 28% of the 298 with poor control

The study indicates that retinopathy arterial calcification and nephropathy are much less common at all stages of diabetes in patients with the disease under good or excellent control Therefore late complications can be prevented or postponed only by careful and continual efforts to control the disease

[With good control diabetic complications are generally less frequent or severe However there is not a good correlation in all instances Indeed some of the same types of [illegible] and severe diabetes poorly con[illegible] cant complications —Ed.]

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(2) D bete 1 449 458 No D 1952
(3) Ibid pp 425 433

lipoproteins ultracentrifugally analyzed in 17 cases of diabetic glomerulosclerosis Cholesterol and phospholipid levels were elevated in most cases There was a marked elevation of the levels of the S_f 12 20 class of lipoproteins in all cases and of S_f 20 35 class of lipoproteins in nearly all The lipoprotein values were markedly elevated even when cholesterol levels were normal The elevation of the S_f 12 20 lipoprotein values was higher than would be expected at the elevated cholesterol levels The study suggests that these classes of serum lipoproteins may be important along with other factors in production of the kidney lesion The elevated S_f 12 30 lipo protein levels may be early evidence of the potential develop ment of glomerulosclerosis

Heparin which reduces levels of the S_f 12 20 classes of lipoproteins was given for six months to three patients with diabetic glomerulosclerosis When it was administered in doses of 100 mg daily S_f 12 20 lipoprotein values were reduced There was a slight elevation in the serum albumin level when it initially was low There was striking clinical improvement Clinical trial with long term heparin administration the low fat diet or both is indicated since reduction of the serum S_f 12 100 lipoprotein values may arrest progress of this fatal kidney complication of diabetes

[That glomerulosclerosis is associated with an abnormality in choles terol metabolism has long been suspected Heparin rapidly changes the status of the lipoproteins but more studies are needed to prove that it is of definite value in atherosclerosis —Ed]

Vascular Complications of Diabetes Relation of Retinal Changes to Other Vascular Complications (Prognostic Value of Diabetic Retinosis) *Jose Antonio Quiroz Herman Villar real Carlos Hernandez Esquivel and Alejandro Sauter*[4] (Mexico City) studied 50 diabetic patients 25 with retinal changes with regard to arterial tension and renal function They found a clear correlation between diabetic retinosis and arterial hypertension It therefore appears that patients with hypertension are more apt than others to present retinal changes Similar facts were established with regard to renal function Intensive study of 30 other patients with retinosis showed that renal dysfunction and arterial hypertension in creased in proportion to the severity of the retinal changes The close correlation between severe retinal lesions and pro nounced renal injury secondary hypertension and poor gen

(4) Re nvest. clin 4 375-388 October 952

eral condition gives diabetic retinosis a distinct prognostic value

The authors present the following classification for retinal changes grade 1 venous engorgement—probable diabetes of 5 years duration grade 2 venous engorgement punctiform hemorrhages microaneurysms and occasional scattered exudates—probable diabetes of more than 10 years duration grade 3 marked venous engorgement grade I arteriolar sclerosis compression at the arteriovenous crossings and more extensive hemorrhages and exudate—long standing diabetes with renal impairment arterial hypertension and probable myocardial sclerosis and grade 4 pronounced venous engorgement with severe changes in vascular caliber grade II arteriolar sclerosis uniform general narrowing localized constriction and irregularity in caliber decided compression at the arteriovenous crossings still more extensive hemorrhage and exudate and some vascular infarcts—diabetes of more than 15 years duration with renal complications poor general condition *presence of infection normal or easily controllable* glycosuria and an advanced stage of the general disease

Diabetic Retinopathy Bernard Becker[5] (Johns Hopkins Univ) states that retinal vascular pathology has been greatly advanced by the study of flat preparations of whole retinas (Fig 118) In flat preparations of diabetic retinas stained with periodic acid fuchsin there can be seen great numbers of discrete saccular aneurysmal dilatations of capillaries occasionally thin walled but frequently enclosed in thickened laminated layers of hyaline material In some instances a hyalinized nodule taking the mucopolysaccharide stain almost obliterates the lumen of the capillary The microaneurysms are found mostly in the deeper capillary layer Surrounding these aneurysms are exudates and hemorrhages which are at least partly explained by leakage of proteins and red cells through the walls of the aneurysms Diabetic retinopathy can be found with no evidence whatsoever of arteriolosclerotic or atherosclerotic lesions The pathologic picture of diabetic retinitis is very similar to that of Kimmelstiel Wilson lesions in the kidney

The progress of diabetic retinopathy can be visualized ophthalmoscopically The disease is progressive but there are relapses and remissions at irregular time intervals The earli

(5) A J t M I 37 73 289 A g t 1952

lipoproteins ultracentrifugally analyzed in 17 cases of diabetic glomerulosclerosis Cholesterol and phospholipid levels were elevated in most cases There was a marked elevation of the levels of the S_f 12 20 class of lipoproteins in all cases and of S_f 20 35 class of lipoproteins in nearly all The lipoprotein values were markedly elevated even when cholesterol levels were normal The elevation of the S_f 12 20 lipoprotein values was higher than would be expected at the elevated cholesterol levels The study suggests that these classes of serum lipoproteins may be important along with other factors in production of the kidney lesion The elevated S_f 12 30 lipo protein levels may be early evidence of the potential develop ment of glomerulosclerosis

Heparin which reduces levels of the S_f 12 20 classes of lipoproteins was given for six months to three patients with diabetic glomerulosclerosis When it was administered in doses of 100 mg daily S_f 12 20 lipoprotein values were reduced There was a slight elevation in the serum albumin level when it initially was low There was striking clinical improvement Clinical trial with long term heparin administration the low fat diet or both is indicated since reduction of the serum S_f 12 100 lipoprotein values may arrest progress of this fatal kidney complication of diabetes

[That glomerulosclerosis is associated with an abnormality in choles terol metabolism has long been suspected Heparin rapidly changes the status of the lipoproteins but more studies are needed to prove that it is of definite value in atherosclerosis —Ed]

Vascular Complications of Diabetes Relation of Retinal Changes to Other Vascular Complications (Prognostic Value of Diabetic Retinosis) Jose Antonio Quiroz Herman Villar real Carlos Hernandez Esquivel and Alejandro Sauter[4] (Mexico City) studied 50 diabetic patients 25 with retinal changes with regard to arterial tension and renal function They found a clear correlation between diabetic retinosis and arterial hypertension It therefore appears that patients with hypertension are more apt than others to present retinal changes Similar facts were established with regard to renal function Intensive study of 30 other patients with retinosis showed that renal dysfunction and arterial hypertension in creased in proportion to the severity of the retinal changes The close correlation between severe retinal lesions and pro nounced renal injury secondary hypertension and poor gen

(4) Rev n est cl 4 375 388 O tober 1952

est changes are usually punctate microaneurysms of capil laries seen singly and in clusters in and about the macula These tend to occur in crops becoming more numerous and surrounded by small exudates and hemorrhages True micro aneurysms tend to persist for weeks and months whereas extravasations can resorb in a few days The punctate hemor rhages finally become hyalinized and are then either invisible ophthalmoscopically or are seen as discrete punctate white dots Further progression of the disease leads to larger and more numerous hemorrhages with confluent exudates In ad vanced stages there are scarring of the retina distortion of capillary pattern and new formation of capillaries in the retina Hemorrhages into the vitreous are followed by organization and vascular ingrowth known as retinitis proliferans Con traction of these fibrous bands may lead to retinal detachment All of this can occur in the absence of associated hyperten sion atherosclerosis renal disease or retinal edema

Increased endogenous corticotrophin during pregnancy may play a role in the pathogenesis of diabetic retinopathy In rabbits made diabetic with alloxan and given injections of corticotrophin an ophthalmoscopic picture resembling early diabetic retinopathy can develop It is believed that both the pancreatic lesions and the action of corticotrophin in amounts that are excessive for a diabetic are factors in the development of retinopathy and Kimmelstiel Wilson lesions This hypothe sis has not been fully established The difference between dia betics with Kimmelstiel Wilson lesions and those without can be explained by a relative excess of certain adrenal cortical secretions in the former or a deficiency in the latter

Histologic examination of the adrenals of diabetics with and without Kimmelstiel Wilson lesions revealed lipid laden vacuolated cells in the zona fasciculata of the adrenal cortex in most of those with Kimmelstiel Wilson lesions and in few of the diabetics without The presence of lipid vacuoles indi cates increased cortical activity The immediate cause of death did not appear to explain the correlation of lipid vacuolation of the zona fasciculata with Kimmelstiel Wilson disease

The absence of lipid vacuoles in the uncomplicated dia betic may perhaps be interpreted as a compensatory decrease in adrenal cortical capacity for certain activities Normal or relatively excessive adrenal cortical capacity in the diabetic would then characterize or perhaps be related to the cause of



F g 118—Fl t p p t s f h m d bet t a st ed w th pe od acid f ch n. T p gl d t th k wall d p ll y y m B tt m cl ter f p llary aneu y m (C t y f Beck B A n Int M d 37 273 289 A gu t 1952)

emia in those with disease of long duration but no higher incidence in those with more severe diabetes

There were 22 intrauterine and 10 neonatal deaths The causes of the neonatal deaths were congenital heart disease with triloculare biventriculare subarachnoid hemorrhage and Miller Wilson triad intrauterine pneumonia and Miller Wilson triad tetralogy of Fallot subdural hemorrhage erythroblastosis and kernicterus intracranial hemorrhage congenital alveolar dysplasia prematurity with primary atelectasis and intraperitoneal hemorrhage Only three deaths were obstetric and perhaps preventable In 15 of the 22 stillbirths no cause of death could be found Of the fetal deaths 72% had already occurred by the end of the 36th week and 81% by the end of the 37th week An even earlier premature delivery than usually advocated probably during the 35th week might decrease intrauterine deaths

In 14 persons who were seen before the 20th week of pregnancy stilbestrol was started at a dosage of 5 mg at the 7th and 8th weeks The dosage was progressively increased every 2 weeks so that by the 34th week the daily dosage was 150 mg the last medication was taken at the end of the 35th week Stilbestrol appeared to decrease the incidence of fetal mortality and maternal toxemia when these 14 patients were compared with a control group of 23 In the treated group there was a fetal death rate of 19% and a toxemia rate of 18% In the control group there was a fetal death rate of 35% and a toxemia rate of 27%

Skeletal Changes in Adult Diabetics C A Hernberg[7] (Helsinki) investigated histologically the skeletons of 14 diabetics aged 33 75 and compared the results with those in 14 nondiabetics of the same age and sex The diabetics were free from acidosis The degree of osteoporosis was determined by careful estimation of the architecture and thickness of the bone trabeculae The space occupied by pores was determined volumetrically Photographs and x rays of the bones were also used A 30% loss of calcium was the minimum detectable on roentgenograms

Simple osteoblastic osteoporosis was the only finding in almost all the diabetics In those over age 65 the degree of osteoporosis was almost the same as in matched controls whereas in younger diabetics the degree of osteoporosis was

(7) A t m d d 143 1 14 1952

the Kimmelstiel Wilson lesion Adrenal cortical function tests in living diabetics with or without Kimmelstiel Wilson lesions may prove informative The diabetic with retinopathy has an adrenal cortex responsive to exogenous corticotrophin as measured by eosinophil counts whereas the adrenal cortex of some diabetics without retinopathy responds less readily or not at all to this test *Further investigation is indicated*

Diabetes and Pregnancy David Hurwitz and Norio Higano[6] (Harvard Med School) discuss their experiences with 140 pregnancies in diabetics during 1932 1950 Except for 14 patients who received diethylstilbestrol by mouth no patients had any specific therapy other than careful medical management of their diabetes and delivery according to ob stetric indications

A high blood sugar level (over 120 mg/100 cc) at the end of a three hour glucose tolerance test (100 Gm glucose by mouth) is diagnostic of diabetes Clinical management of the diabetic patient during pregnancy includes a diet of at least 180 Gm carbohydrate 75 Gm protein and fat accord ing to state of nutrition Both protamine zinc insulin and regular insulin are administered to make the urine as free of sugar as possible without provoking hypoglycemia The pa tient is seen weekly and is admitted at the 35th week for study and evaluation by obstetric and medical staff as to time and method of delivery Delivery is pelvic whenever possible Diabetic management during labor is surprisingly easy If labor is prolonged the patient is given fruit juices orally or glucose intravenously If acetonuria develops additional glu cose and insulin are given The mother may need much less insulin in the puerperium and the infant needs no glucose *after birth*

There was a much lower fetal mortality in those requiring no insulin or in those in whom the onset of the disease oc curred during pregnancy than in patients requiring insulin or those whose diabetes preceded pregnancy Beyond this there was *no statistical difference in fetal mortality* between patients with mild and those with severe diabetes or between those with cases of short and those of long duration The in cidence of toxemia was 29% four times the incidence in non diabetic pregnancies There was a higher incidence of tox

(6) N w Engl d J Med 247 305 309 A g 28 1952

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(7) A t m d d 143 1 14 1952

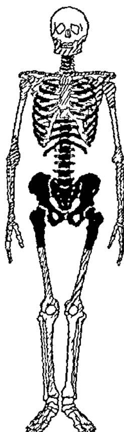


Fig 119—Skeletal distribution of diabetic osteoporosis in one case (Courtesy of H ... b g C A Acta med scand nav 143 1 14 1952)

significantly greater than in controls[7] The skeletal distribution of diabetic osteoporosis as with senile osteoporosis was wide spread (Fig 119) No fibrous osteoclasia was found possibly because none of the diabetics were acidotic It is concluded that osteoporosis occurs fairly regularly as a presenile change in adult diabetics

Quantitative Measurement of Vibratory Perception in Subjects with and without Diabetes Mellitus Using an inaudible electromagnetic vibrator I Arthur Mirsky Perry Futterman and R H Broh Kahn[8] determined the threshold of perception

(8) J Lab & Clin Med 41 1 35 February 1953

of a vibratory stimulus applied to index finger and great toe in 102 patients with diabetes mellitus and in 136 subjects without diabetes Threshold for perception of vibratory stimuli increases with age and the increase is similar on both sides of the body is greater in the toes than in the fingers and is essentially the same in men and women Diabetes impairs vibratory acuity but the influence of age remains unchanged so that the patient with diabetes reacts in this respect as if he were about 20 years older than a person of the same age without diabetes Impairment of vibratory acuity in patients with diabetes is not dependent on either duration or severity of the metabolic syndrome and consequently should be regarded as a concomitant rather than a complication of the metabolic derangement due to insulin insufficiency The diabetes mellitus syndrome in man is due to two independent components one of which results in insulin insufficiency and the other in acceleration of neurovascular damage It is probable that impairment of vibratory perception is due to a diminution of blood supply to the peripheral nerves Acceleration in the development of arteriosclerosis in diabetic persons probably accounts for the decreased blood supply to the nerves

Orthostatic Hypotension in Diabetes Mellitus. Jørgen H Berner Jr[9] (Rikshosp Oslo) points out that many patients with long standing diabetes have diabetic neuropathies some of which are manifested by disorders of the autonomic nervous system Postural hypotension which has been considered due to an autonomic nervous system disturbance was investigated The blood pressure and pulse rate of normal subjects and a number of diabetics were taken when they were recumbent and on standing immediately after rising

Of seven normal subjects one showed a slight initial fall in systolic blood pressure after rising but none had a fall in diastolic levels In seven patients with recently detected diabetes or diabetes without evidence of complications the blood pressure behaved as in the controls except in three patients with slight hypertension Of seven patients with long standing diabetes but no neuropathy five had a slight initial fall in systolic pressure and four of these had a simultaneous slight fall in diastolic level

All of seven patients with long standing diabetes with

(9) A t m d sca d na 143 336 340 195

neuropathy had a definite fall in both systolic and diastolic pressure when they stood up and six had an increase in pulse pressure at the same time All stated that they often felt dizzy on rising in the morning In these patients diabetic neuropathy was evidenced by abnormal pupillary reflex abnormal bowel function and paresis of the rectum and bladder

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LIPID METABOLISM

Review Regulation of Blood Cholesterol is discussed by Sanford O Byers Meyer Friedman and Ray H Rosenman[1] (Mount Zion Hosp San Francisco) The mean plasma choles terol level is higher in man than in other mammals and seems to rise progressively from birth to middle age declining slightly thereafter Sex has no effect on the human blood cholesterol level except that women usually show a higher value during pregnancy About 90% or more of the plasma cholesterol is carried in the form of lipoprotein *molecules* which consist in general of more or less strongly bound ag gregates of cholesterol cholesterol esters various phospho lipids neutral fats and proteins

The cholesterol content of plasma at any instant is the result of four processes and their possible interaction ab sorption synthesis excretion and destruction or conversion of cholesterol The normal plasma cholesterol content appears to be chiefly regulated by the liver which manufactures and discharges cholesterol into plasma then later removes and destroys or converts it into cholic acid (cholate) and perhaps other substances The processes of intestinal absorption and excretion appear to play a minor *even negligible role* in con trol of plasma cholesterol content The processes of synthesis and destruction of cholesterol (both occurring in the liver) appear to be chiefly responsible for the plasma concentration of cholesterol Marked plasma cholesterol changes however appear to be mediated only by the hepatic process of destruc tion of cholesterol Only when there is almost complete *inhi* bition of synthesis as might occur in severe hepatocellular disease might there be a marked change in plasma cholesterol content due to an initial change in rate of its synthesis in the liver

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(1) Metabolism 1 4 9 503 November 1952.

Hypocholesteremia occurs in severe hepatocellular disease hyperthyroidism and in some cases of anemia chronic mal nutrition and idiopathic steatorrhea With the single exception of severe hepatocellular damage plasma cholesterol content is never profoundly or invariably reduced in any disorder

The fundamental cause of hypercholesteremia occurring in both liver and renal disease perhaps in almost all hyper cholesteremic disorders appears to be a reduction in the rate of cholesterol destruction caused by an intrinsic change in the cholesterol binding properties of the plasma protein com plex This change can occur in at least two ways—by altera tion in cholesterol adsorption power of the existing proteins induced by various surface active substances of which cholate appears to be one or by a quantitative change in the constituents of the plasma protein fraction with a resultant increase in the adsorptive power of the total protein complex Hypercholesteremia is seen in extrahepatic biliary obstruc tion intrahepatic biliary obstruction primary biliary cirrho sis acute intrinsic hepatocellular disease von Gierke s disease hypothyroidism diabetes mellitus and occasionally in Addi son s disease pregnancy the nephrotic syndrome primary essential xanthomatosis and idiopathic (familial) hyper lipemia

The blood itself is important in regulation of plasma cholesterol A subject changes from a normocholesteremic to a hypercholesteremic state because the normal rate of passage of cholesterol out of the blood is decreased by preceding changes in plasma proteins The mechanism of the hindrance that makes cholesterol less readily available for removal from the blood lies in the increased power of the plasma lipopro teins to adsorb and thus retain cholesterol This concept ex plains why there has been a failure heretofore to detect in various hypercholesteremic states any change in the rates of absorption excretion or synthesis of cholesterol that could explain the pathogenesis of cholesterol accumulation It ex plains also why there is so often the excess accumulation in hypercholesteremic plasma of other substances (e g phos pholipid various fatty acids and neutral fat) which also de pend on the adsorptive capacity of the plasma protein for their solubility and retention in plasma The concept also ex plains why hypercholesteremia is a state in which only the plasma contains a surplus of cholesterol

The role of the liver in the pathogenesis of hypercholesteremia is essential but indirect in that the liver either furnishes the substance(s) changing the absorptive capacity of plasma proteins or produces a greater quantity of those proteins able in themselves to bind and retain greater quantities of cholesterol

Lack of Effect of Administered Estrogen on Serum Lipids and Lipoproteins of Male and Female Patients S J Glass H Engelberg R Marcus H B Jones and J Gofman[2] (Univ of California) *gave 16 men (50 70) and 15 women (42-65)* estradiol orally in physiologic doses for three months The values for serum cholesterol phospholipids total lipids and S_f 12 20 and S_f 20 100 lipoproteins were determined before therapy and at monthly intervals afterward There was no evidence that estradiol in the doses used caused any reduction in the serum lipids or low density lipoproteins

The study indicates that the relatively lower S_f 12 20 lipoprotein values found in young women as compared with those in men of the same age (a finding that parallels the higher incidence of atherosclerosis in younger males) may not be due to the effect of physiologic amounts of estrogenic hormone on the serum lipids

[It is of interest to note that these authors using an approach somewhat different from Barr s (this YEAR BOOK p 392) did not observe a significant effect on the serum lipids and low density lipoproteins from estradiol therapy Barr *et al* found in patients with advanced atherosclerosis and with demonstrable abnormalities in lipid concentration and distribution that the administration of estrogens caused an increase in the percentage of total plasma cholesterol in the form of alpha lipoproteins and a decrease in the beta lipoprotein fraction with a tendency to reduction in the total cholesterol Upon cessation of estrogen therapy these changes reverted —Ed]

The Liver in Obesity Samuel Zelman[3] (Winter V A Hosp Topeka Kan) conducted a functional and structural study of the status of the liver in 20 obese men (50 100% overweight) aged 23 71 selected after careful screening to exclude all who had past or present illnesses which might affect the liver All 20 patients showed normal dye concentration and emptying of the gallbladder with a Graham Cole test Half had impaired dextrose tolerance but none needed insulin Bromsulfalein retention was abnormal in all patients 10 showed abnormal thymol turbidity of the serum 10 had abnormally high serum cholesterol levels 6 had abnormally high

(2) M tabol m 2 133 136 Ma h 1953
(3) A.M A A ch Int. Med. 90 141 156 A gu t 1952

urobilinogen output 5 had abnormally high serum alkaline phosphatase levels and 4 had abnormal serum cephalin cholesterol flocculation

Needle biopsy of the liver was performed in 19 patients Degenerative changes of the parenchymal cells fatty change bile pigment retention parenchymal cell regeneration and periportal fibrosis was present to at least moderate degree in about half the patients One third had moderate or pronounced cellular infiltration of the periportal spaces No patient had an entirely normal liver

Duration of obesity but not its degree proved significantly related to the extent of anatomic disturbance of the liver Results of liver function tests could not be correlated with histologic findings

Liver damage in obese patients is due to (1) the high caloric requirement of the obese constituting a functional overload on the liver (2) the high carbohydrate high fat low protein diet customary among the obese and (3) the increased requirement of choline and vitamins of the B complex imposed by the quantitative and qualitative nature of the diet of the obese

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BONES JOINTS AND CALCIUM METABOLISM

Experimental Production of Arthritis in Rats by Hypophyseal Growth Hormone William O Reinhardt and Choh Hao Li[4] (Univ of California) adrenalectomized and ovariectomized 18 of 38 plateaued female rats (6 8 months old) and kept the others as controls For six months 10 rats in each group received intraperitoneal injections of gradually increasing daily doses of pituitary growth hormone All were maintained on 1% NaCl drinking water and stock diet After six months the hormone treated animals weighed about 65% more than the untreated normal controls The physical condition of the hormone treated adrenalectomized-ovariectomized animals progressively altered activity became sluggish muscle tone diminished and evidence of knee and ankle joint tenderness with transient episodes of joint swelling appeared Two of these animals were given hydrocortisone for one week and had apparent symptomatic relief and diminution of joint swelling and tenderness

(4) S ∗ 117 295 97 M 20 1953

Roentgen study of all animals at the end of the treatment period disclosed evidence of joint disturbances particularly at the knee characterized by irregularities and erosions of condylar margins localized osteoporotic areas in the condyles and lipping and calcification of joint margins The changes were present in varying degrees in all hormone treated adrenalectomized ovariectomized rats in but one of the hormone-treated normal controls and in none of the untreated controls

The study leads to the hypothesis that the pituitary growth hormone may be of direct etiologic importance in the chronic arthritides and related conditions and that the ameliorative antiarthritic effects of ACTH cortisone and hydrocortisone may be considered to represent either suppression of pituitary growth hormone secretion or antagonism to growth hormone (or to its local effects) at the tissue level or both The experimental evidence described does not preclude the possible existence of sensitization to growth hormone (endogenous or exogenous) or of production of hypersensitivity to other allergenic factors or agents

[The e observations are of great interest and may prove to have distinct significance clinically —Ed]

Prolonged Treatment of Rheumatoid Arthritis with Cortisone and Corticotrophin Melvin H Levin J Bernard Rivo Wayne Scott William G Figueroa Leo Fred and Thomas F Barrett[5] (Univ of California Los Angeles) review experience with cortisone and ACTH in 50 patients with active rheumatoid arthritis of whom 33 had arthritis of the peripheral joints 13 had combined rheumatoid spondylitis and peripheral arthritis and 4 had rheumatoid spondylitis only The patients were followed for as long as 18 months Three therapeutic programs used were (1) ACTH intramuscularly followed by cortisone intramuscularly then by cortisone orally (2) cortisone intramuscularly followed by cortisone orally and (3) only cortisone orally In all groups initial therapy consisted of relatively high doses of hormone for suppression of the arthritis ACTH 80 90 mg intramuscularly daily, was given to 15 patients cortisone 100 200 mg intramuscularly daily was given to 15 and cortisone 100 300 mg orally daily was given to 20 The suppressive treatment was given for 7 30 days Maintenance therapy consisted of ACTH 25 65 mg

(5) Am J M d 14 265 274 M ch 1953

intramuscularly daily to 4 patients cortisone 40 190 mg intramuscularly daily to 25 and cortisone 12 163 mg orally daily to 40

Over all improvement of the patients was inversely proportional to the severity of their disease Those with severe arthritis had only minor improvement and those with minimal arthritis had major improvement Incidence of complete remission remained low even after long term treatment Most patients could be effectively treated in the outpatient department with oral administration of cortisone When cortisone was given orally an average of 20% more was required to effect the same degree of improvement as was obtained by intramuscular administration Many of the patients although not cured by the hormones were greatly improved

Exacerbations of the arthritis occurred with major severity during treatment in 16 patients with moderate severity in 13 and with minor severity in 34 Causes of the exacerbation either were unknown or were due to dose reduction emotional upset infection or cessation of treatment Concomitant reactions other than beneficial occurred in 44 patients In 10 patients therapy was discontinued because of the seriousness of these reactions and 4 patients died In 39 patients one or more of the findings commonly ascribed to hyperfunction of the adrenal cortex developed (e g moon facies hypertrichosis weight gain edema elevated blood pressure sexual disturbances personality changes and diabetes) Many reactions disappeared when the hormone dose was reduced Infections occurred in eight patients (one fatal) delayed wound healing in four psychoses in five duodenal ulcers in three active renal disease in three and vascular changes in three

Until more information is available concerning their hazardous potentialities it is probably inadvisable to use cortisone and ACTH over protracted periods in arthritic patients other than those who have progressive disease despite adequate trial of more conservative therapy

Rheumatoid Arthritis Hydrocortisone is probably the principal glycogenic steroid secreted by the adrenal cortex and under conditions of stress may participate more than cortisone in physiologic reactions Hydrocortisone is twice as potent as cortisone Edward W Boland[6] (Los Angeles)

(6) C l f M d 77 1 6 July 195

studied the effects of two forms of hydrocortisone the free alcohol preparation and the acetate given systemically to patients with rheumatoid arthritis Free alcohol hydrocortisone was given to 10 patients in doses of 100 mg/day The pattern of improvement was similar to that with cortisone but onset of improvement and subsequent improvement were much more striking Free alcohol hydrocortisone was substantially more effective than cortisone acetate when given by mouth in similar doses Hydrocortisone acetate was given eight patients and the effects were inferior to those expected from cortisone acetate in similar doses

Comparisons of potency made by determining maintenance dosage requirement for equivalent degrees of clinical control in the same patients indicated that the effectiveness of free alcohol hydrocortisone is more than 50% greater than that of either the free alcohol or the acetate form of cortisone and about twice as great as that of hydrocortisone acetate The greater antirheumatic activity of free alcohol hydrocortisone is not accompanied by a correspondingly greater tendency toward endocrine complications

Intra articular injection of hydrocortisone acetate appears to have only a limited place in therapy but may be used for temporary relief Results observed in the treatment of osteo arthritis by this method were poorer than in rheumatoid arthritis

Corticotrophin, Protamine Supplement and Plasma Fibrinogen Levels in Chronic Arthritis Earl A Peterman[7] (Providence Hosp Detroit) gave sustained corticotrophin therapy to the point of cortical overstimulation for 8-54 weeks to 26 patients with chronic arthritis mostly rheumatoid All patients showed worthwhile improvement although none had complete clinical remission All had persistent increase in plasma fibrinogen level The increased plasma fibrinogen values so commonly seen in patients with rheumatoid arthritis may be produced by a compensatory mechanism brought into function because of a thromboplastin deficiency resulting from overproduction of heparin or heparin like substances Presence of excessive heparin or heparin like substances in the blood of patients with rheumatoid arthritis is unexplained Neutralization of these substances by protamine sulfate would

(7) J M h g n M Soc 51 1191 1199 S pt mbe 1952

be the most logical way therapeutically to correct the theoretical imbalance in the blood the plasma fibrinogen level should gradually drop to normal as excessive heparin like material is neutralized by intravenously administered protamine sulfate

After the patients had been standardized on corticotrophin therapy and no further drop in plasma fibrinogen level could be expected protamine supplementary therapy 30 100 mg daily was given intravenously with excellent clinical results The plasma fibrinogen level in all patients began to drop toward normal but when protamine was increased beyond the point of ideal maintenance the plasma fibrinogen level rose to new heights only to drop again when protamine was discontinued A similar change was seen in serum glucosamine levels under the influence of protamine Supplementary protamine therapy enhanced partial clinical remission started by corticotrophin in 21 of the 26 patients

Protamine sulfate with corticotrophin may give better clinical results in rheumatoid arthritis than corticotrophin alone Determinations of the serum glucosamine and the plasma fibrinogen levels with the erythrocyte sedimentation rate are useful in evaluating rheumatic disease activity

Metabolic Defect in Gout DeWitt Stetten Jr [8] (New York City) tagged uric acid with radioactive N^{1} and injected it intravenously into four normal subjects who were on a purine free diet rich in protein to preserve nitrogen balance The miscible pool of uric acid (that quantity of uric acid in the body of the subject which is capable of mixing promptly with intravenously injected uric acid and consequently of diluting its isotope) in the four subjects contained an average of 1 131 mg uric acid From estimates of plasma volume and determinations of serum uric acid concentration it was calculated that nearly 1/6 of the uric acid contained in the miscible pool was dissolved in plasma water and 5/6 was in solution in extravascular water From the rate of decline in abundance of N^{15} in urinary uric acid it could be shown that 50 75% of the uric acid in the miscible pool was normally replaced each day by newly formed nonisotopic uric acid This requires that each day 500-850 mg uric acid be introduced into the miscible pool presumably arising largely from oxidation of purines

(8) B ll N w Y k A d Med 8 664 672 O tob 1952

contained in nucleic acid and nucleotides of the body The quantity of uric acid entering the miscible pool exceeded the quantity leaving the pool by the urinary route by 100 150 mg uric acid daily indicating that there is extensive catabolic breakdown of uric acid in the lumen of the gastrointestinal tract

When isotopic uric acid was given patients with gout the miscible pool was greatly increased One patient in whom the pool contained 31 000 mg uric acid was given 2 4 3 6 Gm acetylsalicylic acid daily and after four months the uric acid of the pool was reduced to 2 084 mg There was no change in the level of serum uric acid The magnitude of the miscible pool of uric acid before uricosuric therapy was far greater than could be assumed to exist in solution in the body water in view of the known insolubility of uric acid in water The superficial layers of tophi in gouty patients must contribute to the miscible pool Whereas all uric acid in the miscible pool of a normal person is in solution the largest compartment of the miscible pool in gouty patients is in the solid phase The contraction of the miscible pool after therapy was due to loss of part of the solid phase

The finding that urate in the solid phase contributes to the miscible pool implies that a continuous solution and precipitation of urate is occurring at the interface between tophus and body fluid The deposition of urate in tophi may be considered a reversible process

In both normal and gouty patients ACTH increases the urinary uric acid level accompanied by a fall in the level of serum uric acid The uricosuric effect of ACTH is not at the level of uric production but rather at the level of renal excretion of uric acid ACTH interferes with reabsorption by the renal tubule

Production of uric acid in both normal and gouty patients was studied by observing the rate at which the isotope appears in uric acid when an isotopically labeled precursor was administered Since glycine has been shown to be a specific precursor of atoms 4 5 and 7 of the purine nucleus the amount of N^{15} in urinary uric acid was measured after administration of isotopic (N^{15}) glycine by mouth When isotopic glycine was fed to a normal person the N^{15} concentration in urinary uric acid rose slowly to a maximum after

three or four days and declined gradually thereafter indicating that the isotope was derived from a large and metabolically sluggish pool of labeled purines After 10 days although 30-50% of the isotope administered had been excreted chiefly as urea only about 0 15% had been excreted as uric acid In gouty patients the level of N^{15} in the urinary uric acid rose in two days to a sharp maximum which was about three times as high as in the normal patient Successive N^{15} concentrations in the excreted uric acid declined far more rapidly than was seen in the normal patients The fraction of the N^{15} administered as glycine which appeared in urinary uric acid was larger in the gouty than in the normal patients

In the gouty patient a fraction larger than normal of dietary glycine is utilized for synthesis of uric acid which is promptly excreted in the urine This increased generation of uric acid from dietary nitrogenous precursors operating over a prolonged period is adequate to account for the increase in size of the miscible pool seen in gout The deflection of an abnormally large portion of dietary glycine into uric acid synthesis further exaggerated when the diet is rich in protein and apparently short circuiting the large body reservoirs of purines is reminiscent of the normal situation in birds and reptiles and suggests that the metabolic defect in gout may be attributed to an unusually large uricotelic component in a predominantly ureotelic species

Psoriatic Arthritis Observations on Clinical, Roentgenographic and Pathologic Changes Mary S Sherman[9] (Univ of Chicago) discusses 15 patients 9 males with psoriasis and arthritis In all but two patients there was an interval of several years between onset of the skin changes and appearance of joint symptoms In all patients disease of the nails was present before arthritis appeared The joint symptoms were either insidious or acute In the latter case a finger or toe swelled up in a few hours and became tense livid and shiny Once established the joint syndrome tended to evolve in attacks with spontaneous remissions In the beginning the joints returned to normal between attacks but there was permanent residual damage later (Fig 120) In most patients there was no correlation between severity of the skin disease and severity of the joint involvement nor were their exacerbations and

(9 I B & I S g I A 83 85 O 1 be 195

contained in nucleic acid and nucleotides of the body The quantity of uric acid entering the miscible pool exceeded the quantity leaving the pool by the urinary route by 100 150 mg *uric acid daily* indicating that there is extensive catabolic breakdown of uric acid in the lumen of the gastrointestinal tract

When isotopic uric acid was given patients with gout the miscible pool was greatly increased One patient in whom the pool contained 31 000 mg uric acid was given 2 4 3 6 Gm acetylsalicylic acid daily and after four months the uric acid *of the pool was reduced to 2 084 mg* There was no change in the level of serum uric acid The magnitude of the miscible pool of uric acid before uricosuric therapy was far greater than could be assumed to exist in solution in the body water in view of the known insolubility of uric acid in water The superficial layers of tophi in gouty patients must contribute to the miscible pool Whereas all uric acid in the miscible pool of a normal person is in solution the largest compartment of the miscible pool in gouty patients is in the solid phase The contraction of the miscible pool after therapy was due to loss of part of the solid phase

The finding that urate in the solid phase contributes to the miscible pool implies that a continuous solution and precipitation of urate is occurring at the interface between tophus and body fluid The deposition of urate in tophi may be considered a reversible process

In both normal and gouty patients ACTH increases the *urinary uric acid level accompanied by a fall in the level of serum uric acid The uricosuric effect of ACTH* is not at the level of uric production but rather at the level of renal excretion of uric acid ACTH interferes with reabsorption by the renal tubule

Production of uric acid in both normal and gouty patients was studied by observing the rate at which the isotope appears in uric acid when an isotopically labeled precursor was *administered* Since glycine has been shown to be a specific precursor of atoms 4 5 and 7 of the purine nucleus the amount of N^{15} in urinary uric acid was measured after administration of isotopic (N^{15}) glycine by mouth When isotopic glycine was fed to a normal person the N^{15} concentration in urinary uric acid rose slowly to a maximum after

remissions simultaneous The disease progressed joint by joint Joint symptoms were not accompanied by fever leukocytosis lymphadenopathy iritis cardiac changes or subcutaneous nodules indicating that the joint manifestations were not rheumatoid arthritis

The x ray changes are spectacular There is usually no bone atrophy The earliest changes consist of marginal erosion at the very edges of the phalanges in the interphalangeal joints Later there is irregular destruction extending along the shafts of the bone from the margins so that the cortex appears scalloped and may contain punched out areas Still later gross destruction of the bone ends is evident There is usually little evidence of healing Occasionally there are irregular nodules of new bone formation near involved joints Rarely bony ankylosis occurs In all patients the predilection *for the distal joints of fingers and toes with relative sparing* of the metacarpophalangeal joints was found In the feet the condition started in the distal portions but soon involved all the joints up to and including the metatarsophalangeal These joints became dislocated and the phalanx was displaced dorsally and proximally so that its proximal end came to overlie the distal end of the metatarsal

Biopsies of the joints revealed that there was no pathognomonic pattern and that the pathology varied greatly apparently with the evolutionary age of the lesion Biopsies were taken of 33 involved joints In early lesions the synovial membrane was edematous and showed a generalized chronic inflammatory process In later stages the synovial membrane was thick and injected it had eroded along the edges and had much fibrosis in it At the joint margins chronically inflamed fibrous tissue was seen which eroded cartilage subchondral bone and cortex In later stages there was complete destruction of the joint (Fig 121) Microscopically there was dense fibrous tissue with mild chronic inflammatory changes replacing synovial membrane and periosteum

Treatment of psoriatic arthritis is with cortisone and corticotrophin The hormones do not cure the disease but they induce remissions A good clinical response is obtained with 200 300 mg cortisone or 100 200 mg corticotrophin daily Maintenance doses are 10 50 mg of either drug The hormones also help the skin lesions Patients have been maintained on drug therapy for 6-10 weeks at a time Improvement with hormone therapy has not been permanent





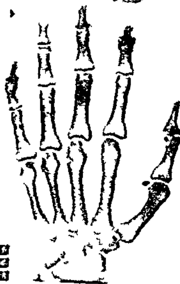




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Fig. 1 [illegible] (bottom) [illegible] fing[illegible] right [illegible] All [illegible]
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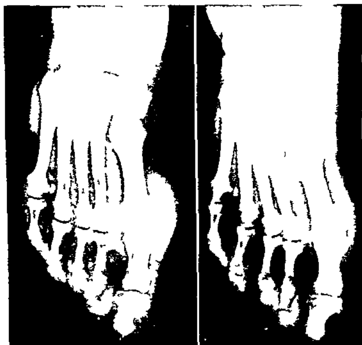
Current Principles of Management in Gout are discussed by Alexander B Gutman and T F Yu[1] (Columbia Univ) Gout as a primary disease is due to a genetically determined inborn error of purine metabolism which is inherited as a single dominant trait with incomplete penetrance particularly incomplete in female carriers The transmitting gene is autosomal not sex linked In some instances there is overproduction of urates and the urinary excretion of urate in gouty subjects exceeds the normal maximum in an appreciable proportion of cases *Uric acid and other purines are elaborated* for the most part by biosynthesis from simple nitrogen and carbon *precursors derived from dietary proteins fats and* carbohydrates as well as by degradation of pre formed purines No primary intrinsic defect in renal excretion has been detected in gouty patients even in those with far advanced renal disease

The cause of acute gouty arthritis is unknown There is no valid evidence that uric acid per se is the offending agent or that gout is an endocrine disease Chronic tophaceous gout is due to precipitation of urates in the tissues as plasma levels rise The urate deposits in the tissues act as foreign body irritants and may cause chronic inflammation The development *of tophaceous deposits is an indication of positive urate bal*ance Visible tophi develop in about 50% of patients with chronic gout

The regulation of gout involves two distinct problems (1) prevention and suppression of attacks of acute gouty arthritis and (2) prevention and mobilization of tophi which represent excessive urate deposition in the tissues The four stages of gout are (1) asymptomatic essential hyperuricemia in which severe dietary restrictions and regular prophylactic therapy are not necessary (2) acute gouty arthritis which calls for early and vigorous treatment with colchicine *ACTH or phenylbutazone singly or in combina*tion (3) intercritical gout the more or less quiescent interval phase *between acute attacks which is treated by regular* colchicine prophylaxis and restriction of diet and (4) chronic *tophaceous gout* which is treated by restricted diet regular prophylaxis to prevent acute recurrences and a uricosuric agent such as probenecid (benemid®)

(1) Am J M d. 13 744 759 Dec mbe 1952

The three uses of colchicine are (1) to terminate established attacks of acute gouty arthritis—divided doses of 0 5 1 0 mg every two to four hours until the attack subsides or diarrhea nausea or vomiting ensue (2) to prevent recurrences of acute seizures in the intercritical periods of chronic



F g 122 (l ft) —B f t tm t h w g l g t d po t soft t t b f g t t w th p h d t

F g 123 (ght) —Aft n y f gul th py f th m t part w th 5 Gm sal cyl t d ly m ked d m t f t d po t n soft tissu a d som l f pu h d t

(Cou t y f G tma A B d Y T F Am J Med 13 744-759 December 1952)

gout—0 5 1 0 mg every two hours on the first intimation of an attack until a total of 3-4 mg has been ingested (3) to prevent recurrences of acute seizures in the intercritical periods of gout—0 5 1 0 mg every night or every other night

The chief use of ACTH in gout is to terminate established attacks of acute arthritis Usually 50 200 mg/day is given for a few days and then the dose is decreased Phenylbutazone

is a potent analgesic and antiphlogistic agent not specific for acute gout but more effective than salicylates It also lowers serum urate levels and usually increases urinary excretion of urate The dose is 0 8 Gm daily The drug has gastrointestinal toxicity Probenecid is a uricosuric agent of low toxicity and is used as such in chronic gout 2 Gm daily rapidly increases urate clearance Indications are that tophaceous deposits can be extensively if slowly mobilized by uricosuric therapy (Figs 122 and 123)

It is important to use restrictive diets to avoid precipitation of acute attacks and to minimize deposition of urate in the tissues

[It is suggested that the reader study the original article Gutman and Yu have carefully evaluated many aspects of the therapy —Ed]

Therapeutic Value of Probenecid (Benemid®) in Gout was studied by Luke R Pascale Alvin Dubin and William S Hoffman[2] (Cook County Hosp) Probenecid reversibly inhibits renal tubular transfer and has uricosuric activity presumably blocking the partial reabsorption of filtered urate A daily dose of 2 Gm probenecid was given to 20 patients with recurrent gout and chronic gouty arthritis and 10 patients were followed for 5 7½ months Serum uric acid levels fell within 72 hours of the first dose to an average of 55% of the control level This fall was associated with an initial 35 200% increase in urate excretion Urate clearance remained increased two to fourfold with continued probenecid administration In three patients with decreased renal function probenecid therapy produced no fall in the serum uric acid level With continued therapy normal levels of serum uric acid could be maintained

Probenecid was given 16 patients for an extended period Eight patients had marked progressive improvement in joint motion five others showed comparable but less dramatic improvement Probenecid therapy proved of greatest benefit in chronic gouty arthritis Joint movement improved and pain and swelling subsided Some patients had acute attacks of gout soon after treatment was started but incidence diminished with continued therapy Attacks occurred mostly in patients who had had them frequently before probenecid therapy and who had chronic gouty arthritis with multiple urate deposits

Evaluation of results of therapy was difficult in eight

(2) J A M A 149 1188-1194 July 6 1952

patients who had acute recurrent gout Only three had acute attacks during therapy but all had lowered serum uric acid levels Probenecid had no effect on joint symptoms during an acute attack of gout

Acetylsalicylic acid given with probenecid completely suppressed the effect of probenecid and the blood urate level remained at least as high as that without any medication This fixation of the serum uric acid level by acetylsalicylic acid is almost certainly due to a blocking or the uricosuric action of probenecid

There were few side effects of probenecid therapy One patient had mild hematuria from urate crystals during the first stage of treatment No significant or consistent changes occurred in concentration of serum electrolytes during prolonged therapy No abnormalities in blood cell distribution were found Results of hepatic and renal function tests remained normal

Probenecid therapy attacks the problem of gout at the level of renal excretion and has no effect on specific gouty response to urate deposition Probenecid is apparently the most effective and most harmless uricosuric agent so far discovered It produces a large negative balance of uric acid when first administered at a time of high serum uric acid levels and a continued small negative balance when the serum level has been lowered to near the upper limit of normal

Primary Hyperparathyroidism Rosemary Murphy Lewis M Hurxthal and George O Bell[3] (Lahey Clinic) report 25 cases of hyperparathyroidism 24 proved at surgery and 1 at autopsy The pathologic diagnosis was single adenoma in 24 and hyperplasia of the parathyroid gland in 1 The physiologic effect of an excess of parathyroid hormone is an increase in the transport load of serum calcium with production of systemic symptoms caused by elevated serum calcium level and secondary symptoms from deposition of calcium in certain tissues and withdrawal of calcium from the bones

The 25 patients (19 women) were aged 16-74 with 56% 30-60 The 24 adenomas were located in the right inferior lobe of thyroid (12) left inferior lobe (5) right superior lobe (3) left superior lobe (2) low in the neck on left (1) and mediastinum (1) The other patient had hyperplasia of all

(3) A M A A h I t M d 89 83 96 M y 195

four glands The adenomas were yellow brown or gray and all were encapsulated with invasion of the capsule in one instance Histologically the tumors consisted of chief cells predominantly or were of a mixed cell type

There was wide variation in presenting symptoms (table) Bone disease was present in 20 patients and 4 had cysts of the mandible The lamina dura examined in 11 patients was absent in only 5 It was present in five patients whose bone disease was not evident and in one whose skeletal involvement was slight and of short duration Hyperparathyroidism occurred with Paget's disease in two patients Previous mistaken

INCIDENCE OF COMPLAINTS

COMPLAINTS	No
Systemic symptoms	
Weakness fatigability	10
Gastrointestinal	9
Muscle pain	5
Weight loss	3
Genitourinary symptoms	
Renal colic	7
Frequency nocturia	6
Polydipsia	5
Hematuria	1
Dysuria	1
Bone symptoms	
Bone pain	13
Deformities	4
Loss of stature	4
Lump in jaw	4
Fractures	2

diagnosis of giant cell tumor of bone had been made in three instances Osteitis fibrosa cystica was present in 11 patients 9 had minimal or atypical bone changes and 5 had no skeletal disease Renal calculi were present in 12 patients

There is a wide range in blood values The blood calcium content may not be markedly elevated A lowered serum protein level may mask an otherwise elevated serum calcium level Renal insufficiency may cause elevation of phosphorus value with or without an associated depression of calcium value In absence of bone disease alkaline phosphatase value is normal If Paget's disease is coexistent the phosphatase level may be excessively high

The chief postoperative complication was tetany seen in 13 patients It was more common in those whose preoperative calcium and alkaline phosphatase levels were very high

A follow up study of the patients from less than 1 year to 18 years after surgery revealed an excellent response to treatment.

[Considerable controversy has existed as to whether parathormone exerted its main action on the kidney or on the bone and/or serum Stewart and Bowen (Endocrinology 51 80 1952) have recently reported evidence indicating that the main action is on the bone —Ed]

Certain Physiologic Responses to Intravenous Injection of Calcium Salts into Normal, Hyperparathyroid and Hypoparathyroid Persons John Eager Howard Theda R Hopkins and Thomas B Connor[4] (Johns Hopkins Univ) found that intravenous administration to normal persons of calcium salts (15 mg /kg body weight in four hours) resulted in a rise in serum inorganic phosphorus concentration and a reduction in urinary excretion of phosphorus The latter is believed best explained by the shutting off of parathyroid hormone secretion in response to hypercalcemia However the rise in serum phosphorus levels was too great to be accounted for entirely by reduction in urinary phosphorus excretion When the intravenous calcium test was given to five patients with parathyroid adenomas they responded with smaller rises in the concentration of serum phosphorus than the normal subjects and with either a lesser reduction or an increase of urinary phosphorus excretion Three patients with surgical hypoparathyroidism responded to the test with greatly increased urinary phosphorus excretion Two patients tested *within a few days after removal of parathyroid adenomas* had responses in the hyperparathyroid range despite normocalcemia but the same patients and three others had normal responses when tested two weeks to six months after operation

The difference in the response to calcium administration of serum and urinary phosphorus levels of the normal subject and those of patients with parathyroid dysfunctions is seen in Figure 124 The rise or fall of serum phosphorus levels in mg / 100 cc at eight hours after beginning the test is plotted to the left of the midline Equidistant to the right of the midline is plotted the rise or fall of urinary phosphorus levels in percentile variation from a control period The curves in the normal group are parallel In the hyperparathyroid group no curve slopes down as sharply as do any of the normal curves All curves in the hypoparathyroid group go up

(4) J Clin. Endoc 13 119 J ry 1953

✓ The study shows that urinary phosphorus excretion falls despite the rise of serum phosphorus level when calcium salts are administered to normal individuals and strengthens the hypothesis that normal parathyroid functional activity is governed by the calcium concentration of the extracellular fluid The parathyroid hormone influences renal reabsorption of inorganic phosphate The function of normal parathyroid glands is suppressed by a functioning adenoma in weakly functioning tumors the normal glands may be still further

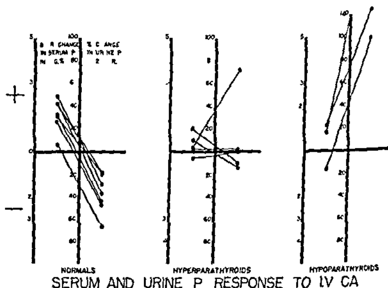


Fig 1 4 (Court y f H w rd J E et al J Cl n Endoc inol 13 1 19 Ja ry 1953)

suppressed by the hypercalcemia resulting from the test or the tumor may be partly under control of the calcium concentration in its environment The urinary phosphorus excretion of the hypoparathyroid patients is difficult to interpret These patients may have hypocalcemic rickets

The rise in serum phosphorus levels in normal subjects cannot be accounted for by the reduced urinary output of phosphorus The source of the phosphorus which brings about the rise in serum concentration is unknown but perhaps elevation of the serum calcium level per se causes a shift of cellular phosphate to the extracellular compartment Such a

shift would most likely result from an effect on a phosphate enzyme system

[An interesting observation that should be advantageous especially in diagnosis of ome patients without definitely abnormal blood values —Ed]

Usefulness of Strontium as Adjuvant to Calcium in Remineralization of the Skeleton in Man is discussed by Ephraim Shorr and Anne C Carter[5] (Cornell Univ) Previous experiments have shown that Sr can influence the bony skeleton and can replace Ca in various physiologic processes Tracer studies using radioactive Sr have shown that the movement of Sr in and out of the skeleton parallels that of Ca under the influence of such agents as parathyroid hormone and vitamin D Strontium is deposited very slowly in the skeleton and deposition can be accelerated by small amounts of Ca Strontium can be utilized by man without hazard and has the special property of stimulating unusually abundant production of osteoid tissue

To assess the possible value of Sr as an adjuvant to Ca in remineralization of the depleted skeleton Sr was given to 12 patients (all with skeletal demineralization) who had various disturbances of bone metabolism including postmenopausal and senile osteoporosis idiopathic osteoporosis Morquio s disease and Milkman s disease The patients were given diets containing known calcium phosphorus and protein content Strontium lactate was given orally Studies were made of effects of agents e g vitamin D androgens and estrogens known to enhance Ca deposition Except for relatively short *periods during which 27 Gm Sr was given daily* standard daily dose was 6 4 Gm Sr lactate equivalent to 1 75 Gm Sr, which was taken continuously for as long as four years without ill effects The Sr lactate was retained well and retention was generally as great as and usually much greater than that of Ca Calculations of phosphate retention taking place with Sr storage indicated the stoichiometric relation expected if Sr were deposited chiefly as tristrontium phosphate Calcium retention was not reduced during storage of Sr Effects of Sr were additive in terms of total Ca and Sr deposition *Strontium retention was increased by vitamin D androgens* and estrogens

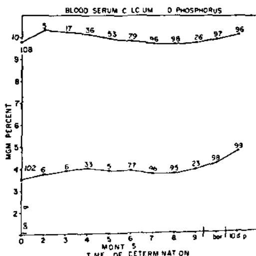
When Ca was given in doses large enough that a retention ceiling was reached additional Sr was retained When Ca and Sr were given in optimal amounts combined retention was far

(5) B H H p J 1 D 13 59 66 Ap 1 1952

greater than retention of Ca alone no matter how high the Ca intake This combined retention indicates that a doubling and often *a tripling of the rate at which the skeleton can be* remineralized may be anticipated

Strontium favorably influences *the clinical course of the* patient with osteoporosis and radioactive Sr can serve usefully in studies of bone metabolism

Further Observations on Serum Calcium and Phosphorus in Pregnancy Robert L Newman[6] (Univ of Kansas) administered four types of calcium and vitamin D medications to



F g 125 (Courte y f Newman R L Am. J Ob t & Gy e 65 796 803 Ap il 1953)

groups of women during pregnancy labor and puerperium The average normal curve for serum calcium and phosphorus levels during pregnancy shows a slight reduction in values most pronounced in the seventh and eighth months rising through the ninth month labor and the first 10 days post partum to its original level (Fig 125) The medications were 1 5 Gm calcium daily 2 2 Gm calcium and 1 500 units of vitamin D daily 2 6 Gm calcium and 600 units of vitamin D daily and 1 7 Gm calcium and 900 units of vitamin D daily With all types of medication there was no increase *in serum* calcium content but a definite suggestion that it was decreased

(6) Am. J Obst & Gynec. 65 796-803 April 1953

The ionized calcium level ranged persistently at or below the lower range of normal (4 25 5 25 mg/100 cc serum according to McLean and Hastings) There was no correlation between the lower calcium levels and prolonged labor or other labor complications There was even a suggestion that the higher levels of ionized calcium were associated with longer labors In an attempt to check the accuracy of these results the ionized calcium levels in 110 nonpregnant women were calculated and found to be 3 75-4 70 mg/100 cc instead of the higher figures It is suggested that the normal range of calcium is lower than that previously reported

Calcium gluconate given intravenously to 19 women in prolonged labor had no apparent influence on the labor It is doubtful that calcium benefits pregnant women

[These studies like those of many other chemical values in pregnancy demonstrate that the *normal* values may deviate somewhat from the non pregnant normal range —Ed]

MISCELLANEOUS

Neurogenic Hypernatremia and Hyperchloremia are usually associated with lesions of the frontal lobes or hypothalamus Irving S Cooper (New York Univ Post Grad Med School) and Paul H Crevier[7] (New York Univ Bellevue Med Center) add 4 cases to the 14 already reported

CASE 1 —Infant aged 9 months was retarded mentally and physically The EEG showed diffuse bilateral abnormalities When examination of the cerebrospinal fluid showed chlorides of 152 mEq/L (normal 125 mEq) serum levels were measured they were similarly elevated for sodium and chloride Blood studies showed no hemoconcentration and there was no clinical evidence of dehydration

*CASE 2 —Infant aged 3 months with enlarged head had bi*lateral subdural hygromas Serum sodium content was 155 mEq/L (normal 131 141 mEq) and plasma chlorides 122 mEq (normal 96-103 mEq) Bilateral trephine drainage of the hygromas was followed by subdural drainage for 48 hours During the next week blood chemistry became normal

CASE 3 —Woman 58 had had Torkildsen ventriculocisternostomy for suspected brain tumor of the third ventricle at age 55 A revision of the tube three years later failed to relieve hydrocephalus so she had *transventricular removal of a fibroblastic meningioma.* She had postoperative hypotension hyperthermia and coma and died on the seventh day During the week after operation she had received 2 500 cc fluid daily by Levin tube sodium and chloride

(7) J Cl n E doc ol 12 821 830 J ly 1952

values which preoperatively had been within normal limits rose above normal despite adequate intake and output Serum potassium levels were unchanged

CASE 4 —Woman 56, had partial removal of a craniopharyngioma which involved the optic chiasm anterior cerebral arteries and floor of the third ventricle In the five months thereafter she became progressively lethargic and died Two months after surgery plasma chloride values rose to 118 mEq/L in the next two months on regular diet the values ranged from 103 to 130 mEq Even with a salt free diet the level ranged from 112 to 125 mEq Serum sodium concentration ranged from 139 to 152 mEq during the five months but potassium levels gradually dropped from 4 1 to 3 4 mEq (normal 4 5 mEq) During this period there was adequate diuresis and no clinical evidence of dehydration or hemoconcentration

The pathogenesis of elevated serum sodium and plasma chloride values is unknown The authors believe the cause to be interference with a cerebral osmoreceptor mechanism Perhaps the high death rate after operations in the region of the third ventricle and hypothalamus may have some relation to this mineral upset especially since it has been shown that death can result from experimentally induced hypertonicity of extracellular fluid

Modifications of Electrolyte Metabolism and Renal Function by Pyrazole Derivatives was studied by P Dupont A Duckert Maulbetsch and J Fabre[8] (Geneva) using two analgesic and antiphlogistic preparations irgapyrine (15% solution of dimethylaminoantipyrine and sodium dioxydiphenylbutylpyrazolidine in 5 ml ampules) and butazolidin* (20% solution of sodium dioxydiphenylbutylpyrazolidine in 5 ml ampules) Dosage averaged 1 ampule a day intramuscularly An average weight increase of 0 86 lb which reached a maximum after nine days was noted in 90% of 88 patients under medication In six patients receiving irgapyrine and three receiving butazolidin* neither drug affected potassium excretion both caused chlorine sodium and water retention as weight increased After 10 days of treatment retention and weight diminished When treatment was stopped marked diuresis and salt water and weight loss followed Retention was especially high in patients with functional deficiencies of heart kidneys or liver causing edema and dyspnea that ceased when treatment was stopped Intramuscular administration had a more marked effect on retention than oral or

(8) H I et med. acta 6 528-546 Dec 19 1952

rectal administration Irgapyrine given intramuscularly had no marked effect on glomerular filtration measured by the creatinine clearance test in 11 patients indicating that chlorine and sodium retention is due to tubular reabsorption Given intravenously to four patients it caused a more marked reduction of creatinine clearance which reached a minimum between 60 and 150 minutes after injection

In the absence of renal damage or lesions the authors conclude that the compounds tested have a functional action — Injection of a mercurial diuretic (salyrgan®) on the third day of irgapyrine treatment in 21 patients had almost no effect suggesting that pyrazole derivatives have an antagonistic action against mercurial diuretics

Bodily Changes in Surgical Convalescence I Normal Sequence — Observations and Interpretations Francis D Moore[9] (Harvard Med School) describes four phases of normal convalescence after surgical trauma which are viewed as an orderly sequence in which emergency mechanisms (circulation energy) are first replaced by wound healing then by digestion regrowth of other tissues and reproduction as the top priorities for the organism The duration of each phase depends on the extent and duration of the trauma for extensive anastomotic gastrointestinal surgery the four phases last about 5 4 20 and 40 days respectively

I The adrenergic corticoid phase —This phase begins when the patient goes to the operating room and anesthesia is induced Clinically there is evidence of adrenal medullary activity increased pulse rate narrowing of pulse pressure peripheral vasoconstriction—with or without sweating—and rise in blood sugar level There is apprehension before and after the trauma After surgery the patient is listless and does not turn in bed intestinal peristalsis ceases within 12 24 hours he is not interested in his environment and has no hunger The temperature is elevated two to three days There is relative oliguria the day of operation and during the following days outputs of 1 000 2 000 cc are not unusual The first clinical evidences of the end of the corticoid phase are a return of peristalsis expelling of flatus by rectum onset of hunger and gradual return of interest in the outside world There is little wound healing Weight drops rapidly due to

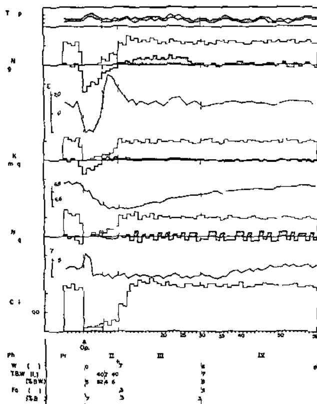
(9) A Su g 137 289 315 M h 1953

rapid utilization of body fat Nitrogen excretion is increased in proportion to the severity of the trauma There is a negative balance of potassium The sodium excretion on the day of operation is reduced almost to zero Caloric intake is low the eosinophil count is low and the sodium content of the blood falls Total body water content changes only slightly The rise of eosinophils to a high level and lowering of urinary nitrogen excretion indicate the end of phase I

II The corticoid withdrawal phase—This phase begins about the fourth day and lasts two to three days There is renewed interest in the outside world and there is water diuresis The wound ceases to be painful and considerable fibroblastic proliferation occurs Tensile strength increases and the sutures can be removed There is further weight loss The nitrogen balance slowly returns to positive Potassium loss in the urine diminishes A positive potassium balance returns sooner than a positive nitrogen balance There is a diuresis of sodium Caloric intake increases The eosinophil count rises and then returns to normal Blood sodium level returns to normal There is minor drop of total body water content associated with diuresis The cessation of rapid potassium loading and sodium diuresis a day or two after the backswing overshooting of eosinophils indicates that phase II is over

III Spontaneous anabolic phase—This phase is initiated by adequate oral diet It begins about the seventh to tenth day after major peritoneal injury The patient has increased strength and is hungry He has more interest in outside activities but his strength is still impaired Blood chemistry and urine output are normal Tensile strength of the wound is almost normal There are weight gain a steady positive nitrogen balance and high caloric intake There are weak positive potassium balance zero sodium balance and normal eosinophil count The excretion of 17 ketosteroids is low Total body water content increases

IV *The fat gain phase—This phase may last many* weeks or months and occurs when the patient is at home There is a return of full bodily weight and function Sexual interests and menses return There is a marked gain in weight The wound becomes white and local activity ceases There is zero balance of nitrogen potassium and sodium Caloric intake is high The eosinophil count remains normal Total body water



F g 1 6—Norm l p t al 6 7 t ma M t bol b lan e of t g p t m d sod m h w t geth w th ph l t body w ht 17 k to t d t (mg /24 hr) d cal tak N g t b l n ha t d wh te bel w l d l d bl k l th th h d d bl ck th t th h t bt d d bel w th tak lw y p s t t on wh th p t e g u b l lt B l w th h t e h wn w ght t tal body wat ont t (lt g a d p t f body w ght) d f t (s k l gr m d p r t f b dy w ght) Th a th d t p wh h th b dy mp t n h g b d t l b ok l d t tra t p ods b tw the f ph (C t y f Moo F D A S g 137 289 315 M h 1953)

content remains normal The completion of the fat gain phase is signaled by the return of body weight to normal and at this time metabolic convalescence appears to be complete

The endocrinology of the four phases is as yet poorly understood It is important to conceive of convalescence as the net resultant of interlocking and sequential biologic forces

rapid utilization of body fat Nitrogen excretion is increased in proportion to the severity of the trauma There is a negative balance of potassium The sodium excretion on the day of operation is reduced almost to zero Caloric intake is low the eosinophil count is low and the sodium content of the blood falls Total body water content changes only slightly The rise of eosinophils to a high level and lowering of urinary nitrogen excretion indicate the end of phase I

II The corticoid withdrawal phase —This phase begins about the fourth day and lasts two to three days There is renewed interest in the outside world and there is water diuresis The wound ceases to be painful and considerable fibroblastic proliferation occurs Tensile strength increases and the sutures can be removed There is further weight loss The nitrogen balance slowly returns to positive Potassium loss in the urine diminishes A positive potassium balance returns sooner than a positive nitrogen balance There is a diuresis of sodium Caloric intake increases The eosinophil count rises and then returns to normal Blood sodium level returns to normal There is minor drop of total body water content associated with diuresis The cessation of rapid potassium loading and sodium diuresis a day or two after the backswing overshooting of eosinophils indicates that phase II is over

III Spontaneous anabolic phase —This phase is initiated by adequate oral diet It begins about the seventh to tenth day after major peritoneal injury The patient has increased strength and is hungry He has more interest in outside activities but his strength is still impaired Blood chemistry and urine output are normal Tensile strength of the wound is almost normal There are weight gain a steady positive nitrogen balance and high caloric intake There are weak positive potassium balance zero sodium balance and normal eosinophil count The excretion of 17 ketosteroids is low Total body water content increases

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for pulmonary tuberculosis These patients receiving no parenteral therapy other than blood replacement during operation were able to maintain adequate urinary outputs postoperatively despite low oral fluid intake They received small amounts of fluid orally during the first 24 hours after operation and all fluid and nourishment by mouth throughout the postoperative period Postoperative sodium retention was pronounced Serum chloride and sodium levels and CO_2 combining power were normal postoperatively Serum potassium content and urinary potassium excretion remained normal Underestimation of blood replacement at operation led to deficits in plasma volume and total circulating proteins in the early postoperative period

In all patients the extracellular fluid compartment was expanded postoperatively probably due to salt retention This indicates that saline should not be given after thoracic surgery to patients with poor pulmonary reserve and pulmonary hypertension and anoxia because of danger of pulmonary edema More blood given during surgery would probably have largely corrected the deficits in hematocrit value and total circulating protein and blood volumes in the early postoperative period

Metabolic Disorder in Hepatolenticular Degeneration. W B Matthews M D Milne and M Bell (Manchester Univ) describe two juvenile cases of progressive lenticular degeneration with slight evidence of hepatic disease and discuss the results of studies of the metabolism and excretion of amino acids and copper Both patients had abnormal amino aciduria in the absence of any detectable increase of the plasma amino acids defective renal tubular reabsorption of amino acids and increased amino nitrogen clearances after the ingestion of glycine and alanine Both had abnormally high urinary excretion of copper further increased by ingestion of BAL glycine or alanine There was considerable correlation between the power of the urine to dissolve copper in alkaline solution and the amount of copper actually excreted (Fig 127) Although the maximal excretion after ingestion of amino acids was similar in amount to that reached after BAL the former would not be an effective means of increasing copper elimina-

( ) Q art. J M d. 1 425 446 O t b 1952

These forces bear not only on the wound as a break in continuity of the organism but also on survival of the organism in acute emergency mobilization of substances to heal the wound during the inevitable period of transient starvation and then reconstruction of the body to accomplish growth and reproduction or *if necessary a new adjustment to injury* The normal human body is geared to negotiate the first two phases without diet The final two reconstructive phases require exogenous diet in adequate amounts for completion

In phase I there is pronounced adrenal medullary activity due to epinephrine and related compounds early in the phase Later there is increased secretion of anterior pituitary corticotrophin with a resultant secretion by the adrenal cortex of steroid hormones In phase II there is less cortical activity The endocrine reaction in phase III may be gonadal or in the nature of a growth hormone response The anabolism in this phase is probably due to some growth hormone stimulation The endocrine factors in phase IV are unknown

The teleology of each phase is different In phase I all activity is directed to the metabolic priorities of the pressor energy catabolism triad All other activity growth reproduction and wound healing ceases All mechanisms are used to maintain circulation energy production and mobilization of cellular material for the wound In phase II all activity is directed toward wound healing digestion growth and reproduction In phase III body activity is directed toward rebuilding body composition and muscular strength The wound increases in strength In phase IV the wound drops to lowest priority and all that *remains to be done is to rebuild the storehouse of* energy called the body fat

The four phases are illustrated in Figure 126

[This classic study helps clarify many of the biochemical and clinical observations associated with surgical procedures and emphasize the important considerations regarding the nutritional status Many a patient has been overtreated with saline —Ed]

Body Fluid Shifts, Sodium and Potassium Metabolism in Patients Undergoing Thoracic Surgical Procedures Elmore M Aronstam Claude H Schmidt and Edward Jenkins[1] (Fitzsimons Army Hosp Denver) studied 20 patients (average age 29 8) who underwent various thoracic operations mostly

(1) A S g 137 316-324 Ma h 1953

from protein bound plasma copper The abnormally high urinary copper excretion in the absence of proteinuria occurs only when there is both increased tissue copper and abnormal aminoaciduria and is almost specific of Wilson s disease Hepatolenticular degeneration exhibits the strange paradox of a disease combining abnormally high retention of copper in the tissues and excessive elimination of the element in the urine

There is no known effective therapy The disease is probably an inborn error of metabolism resulting from a recessive hereditary factor

Metabolism of Iron II Intravenous Iron Tolerance Tests in Laennec s Cirrhosis Stanley E Gitlow Milton R Beyers and John P Colmore[3] (V A Hosp Bronx N Y) performed 28 intravenous iron tolerance tests in patients with Laennec s cirrhosis acute infectious hepatitis and diabetes with hepatomegaly The test permits measurement of the fasting serum iron level (SeFe) as the first specimen the total iron binding capacity (TIBC) as that specimen drawn five minutes after the injection of ferric ammonium citrate and the 120 minute serum iron level The ratio SeFe TIBC represents the degree of saturation of the iron binding protein The increase from SeFe to TIBC is the unsaturation iron binding capacity The decrease in serum iron level from the 5 minute to the 120 minute specimen is apparently a function of the tissue uptake of serum iron In normal subjects there is a fairly constant relation between the increase (INC) and the decrease (DEC) conveniently expressed as the DEC INC ratio

The average SeFe in normal male subjects is 146 μg /100 cc range 74 186 μg The TIBC ranges from 253 to 388 μg /100 cc average 341 μg The average saturation of the serum iron binding protein is normally 41% with a range of 28 58% The 120 minute values average 289 μg /100 cc varying from 163 335 μg The normal DEC INC ratio ranges from 0 10 to 0 50 average 0 26

Intravenous iron tolerance tests in cirrhosis reveal (1) a slightly lower average SeFe value with a greater range (2) an appreciably lower average TIBC level with a spread beginning below but falling partially within the normal range

(3) J Lab & Cl M d 40 541 549 O tobe 195

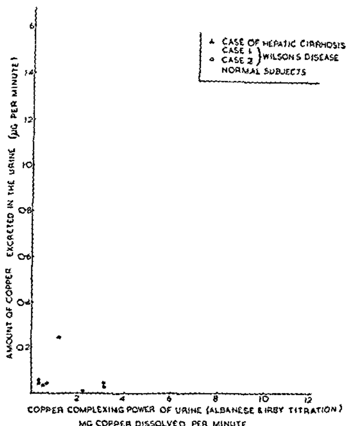


Fig 127—C pac ty of u in to d solve coppe in alkal ne sol t n is eas d after i ge t of gly e o alan ne wh ch inc ease ex tion of coppe n tw cas s of hepat le t cula dege tion b t has n h eff ct n f r no mal s b ject A ca e f h p ti c h nte m d at n th s spe t (C u te y of M tth ws W B f l Q art J Med 21 425 446 O tobe 1952)

tion since it would be impossible to give amino acids in large repeated doses The high basal excretion of amino acids in the disease probably contributes to the increased elimination of copper

Intravenous injection of cuprelone a complex salt containing copper increased the amount of copper excreted although most of the injected copper was temporarily retained in the body

The increased copper excreted in the urine after ingestion of amino acids and BAL is derived from tissue stores and not

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(3) a normal average saturation with a slightly increased range and (4) a slightly higher average DEC INC ratio reflecting an elevated upper limit of the range There is considerable overlap of results of the iron tolerance test in normal subjects and in patients with portal cirrhosis and the test is in no way diagnostic of the latter Test results may be normal in every respect in cirrhosis Anemia may be associated with hypoferremia and bromsulfalein retention with elevation of SeFe values

The intravenous iron tolerance test is a valuable diagnostic aid in the differentiation of Laennec s cirrhosis from hemochromatosis Intravenous iron tolerance tests in hemochomatosis reveal (1) a normal or high SeFe (120 297 μg/100 cc averaging 213 μg) (2) a normal or low TIBC (164-335 μg/100 cc averaging 246 μg) (3) a high degree of saturation of iron binding protein (63 99% averaging 94%) and (4) a high DEC INC ratio (0 59 5 33 averaging 2 09) Saturation and DEC INC ratio appear to be the most important factors in differential diagnosis

In three patients with acute hepatitis there was a high degree of saturation in three and an abnormally elevated DEC INC ratio in one indicating that hepatitis can simulate hemochromatosis insofar as the intravenous iron test is concerned It should rarely be necessary to differentiate hemochromatosis from acute hepatitis by the use of this test In two patients with diabetes with hepatomegaly intravenous iron tolerance was normal

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